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TRICUSPID REGURGITATION IN DIFFERENT LOADING CONDITIONS

Epidemiology, Determinants and Management

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Dissertation presented in partial fulfilment of the requirements for the degree of Doctor in Biomedical Sciences

December 2014

Dankwoord

This thesis wouldn't be realised without the help and support of many, to whom I wish to offer my warm thanks.

First, I would like to express my appreciation and thanks to the members of the jury, Professors Agnès Pasquet, Folkert Meijboom, Marion Delcroix and Bart Meyns for their valuable suggestions and constructive remarks. I would also like to thank Prof. S. Janssens, head of Cardiology and Prof. F. Van de Werf, former head of the Cardiology for providing a scientific framework within and around the clinical training. Furthermore, I would like to thank the IWT (Agency for Innovation by Science and Technology) for their financial support the past four years.

Ik had dit project nooit aangevat, noch tot een goed einde gebracht zonder de hulp van mijn promotor Professor Werner Budts. Met de keuze voor een weinig evident onderwerp, niet direct aansluitend op een bestaande onderzoekslijn, zijn we in een diepe zee gesprongen. Na initieel moeizaam navigeren hebben we het schip toch in de juiste richting kunnen sturen. De inzichten die uit het veelvuldige overleg voortvloeiden hebben nieuwe onderzoekspaden geopend. Uw niet aflatend enthousiasme en optimisme zorgden ervoor dat ook moeilijke momenten omgezet werden in boeiende uitdagingen. Daarnaast was er ruim de mogelijkheid voor eigen initiatief om zo autonoom een aantal ideeën uit te werken en daar zelf de nodige stappen voor te ondernemen. Op die manier heeft u mij de bagage en vooral het doorzettingsvermogen meegegeven die onontbeerlijk zijn om wetenschappelijk onderzoek tot een goed einde te brengen. Ten slotte was u steeds te vinden voor een goed gesprek en goede raad, ook over de "dingen des levens".

Ook mijn copromotoren Professor Paul Herijgers en Professor Jens-Uwe Voigt, wens ik te bedanken voor het vertrouwen dat jullie gaven, de deuren die jullie geopend hebben en de waardevolle feedback op de resultaten.

Alexander, jij hebt me bij de eerste stapjes begeleid. We zaten vaak op dezelfde golflengte en dit niet enkel op professioneel vlak. Ook buiten de wetenschap en de klinische praktijk om ben je steeds te vinden voor een goed gesprek, liefst met een drankje erbij.

Hadewich, ook jij was er die eerste momenten bij en de discussies die we gevoerd

hebben waren steeds verhelderend.

Charlien en Frederik, jullie zijn me het laatste jaar komen vergezellen. Ik ben ervan overtuigd dat jullie het wetenschappelijk werk binnen de dienst congenitale cardiologie een nieuwe boost zullen geven.

Guido, Peter, Ward, Christoph, Lucas, Thomas, Dieter, Jean-Yves en Vincent, samen in hetzelfde schuitje liepen we elkaar regelmatig tegen het lijf. De gesprekken waren steeds motiverend en leerrijk. Andre, your commitment and insights led to my fascination for cardiac hemodynamics.

Valérie, je bood steeds je hulp aan waar mogelijk. Zeker als het logistiek niet liep zoals verwacht, zette je je steeds in om een oplossing te vinden.

Karin, Conny, Rik, Peter, Katleen en Ann, het was een plezier om bij jullie op het LCC te vertoeven. Jullie zorgden op tijd en stond voor een adempauze, dat wil zeggen: tijd voor een stukje taart. Ik kon steeds terecht voor een ontspannend gesprek en de laatste maanden ook voor "opvoedkundige tips van ervaringsdeskundigen." Ann, je was er steeds om mijn eenvoudige "klinische" geest om te buigen in een "statistisch" verstand.

Maaike, dank je voor de hulp tijdens data collectie, maar vooral voor de geanimeerde gesprekken over om het even wat. Misschien delen we nog wel eens een afspeellijst.

Krista, je was de perfecte gids in het administratieve doolhof van de KULeuven. Bij elke vraag kon je me steeds in contact brengen met de juiste contactpersoon, wat me uren telefoneren bespaard heeft.

Monique en de voltallige equipe van functiemetingen, bij jullie leerde ik de echocardiografie. Daarnaast hebben jullie mee helpen zoeken naar oplossingen om ruimte en plaats te voorzien om de testen uit te voeren.

Guido, Stefan en Kris, bedankt voor de hulp met het CMR gedeelte!

Dr. Troost, Sonia, Kristien, Christine, Hilde, Sara, Lizzy en Leen, jullie enthousiasme en inzet maakt de dienst congenitale cardiologie tot wat ze is en samenwerken tot een genoegen.

Roselien, je hebt mij de kneepjes van de inspanningstest geleerd, en je was steeds bereid om mee te helpen aan de oppuntstelling van nieuwe proefopstellingen.

Geen studies zonder bereidwillige patiënten, die meerdere uren opofferden om deel te nemen. Hen wil ik dan ook expliciet bedanken voor hun enthousiasme en hulpvaardigheid.

Een bijzondere dank-je-wel verdienen mijn ouders, broers en schoonfamilie. Allen geschoold en werkzaam buiten de medische wereld, maakten jullie steeds duidelijk dat er een wereld is buiten de ziekenhuismuren. Jullie zorgden voor rustpunten in de soms eenzijdige arbeid die een doctoraat inhoudt en bij problemen en bezorgdheden staan jullie als vanzelfsprekend klaar om me ter hulp te schieten.

Niettegenstaande al het bovenstaande, is het uiteindelijk jij, Anne-Sophie, die de grootste bijdrage hebt geleverd tot het finaliseren van deze thesis. Een doctoraat vindt plaats in een levensfase vol veranderingen. De afgelopen 4 jaar waren dan ook gevuld met veel spannende en nieuwe ervaringen. Dit, gecombineerd met de ups-en-downs van een doctoraat (x2), was zeker niet altijd evident maar je energie, vastberadenheid en af en toe ook een duwtje in de rug hebben mij door de moeilijke periodes heen geholpen. “Uiteindelijk komt alles goed.” In augustus kwam bovendien Lauranne ons vervoegen, en plots zijn we een gezin, niet langer een koppel. De toekomst is misschien nog onduidelijk, maar samen staan we ongetwijfeld voor een boeiende tijd!

Tricuspid Regurgitation in different loading Conditions: Epidemiology, Determinants and Management.

List of abbreviations

aFib=atrial fibrillation
ASD=atrial septal defect
AT=anaerobic threshold
AV=atrioventricular
AVA=aortic valve area
BMI=body mass index
BP=blood pressure
BSA=body surface area
CAD=coronary artery disease
CCB=calcium channel blocker
CMP=cardiomyopathy
CMR=cardiac magnetic resonance
CO=cardiac output
CVA=cerebrovascular accident
CW=continuous wave
FAC=fractional area change
GFR=glomerular filtration rate
HR=hazard ratio
HR=heart rate
HRR=heart rate reserve
IVC=inferior vena cava
LHR=likelihood ratio
LVEF= left ventricular ejection fraction
MI=myocardial infarction
MR=mitral regurgitation
MVS=mitral valve surgery
NPV=negative predictive value
NYHA=New York Heart Association
OR=odds ratio
OUES=oxygen Uptake Efficiency Slope
PAH=pulmonary arterial hypertension
PAP=pulmonary artery pressure
PASP=pulmonary artery systolic pressure
PAT=pulmonary artery systolic flow
PEA=pulmonary endarterectomy
PH= pulmonary hypertension
PIP=peak-instantaneous-pressure
PPV=positive predictive value
PV=pulmonary valve
PVR=pulmonary valvular resistance
RA=right atrium
RAP=right atrial pressure
RER=respiratory gas exchange ratio
RHC=right heart catheterization
ROC=receiver operator characteristics
RV=right ventricle
RVP=right ventricular pressure
TA=tricuspid annuloplasty
TAPSE=tricuspid annular plane systolic excursion
TIA=transient ischaemic attack
TR=tricuspid valve regurgitation
TV=tricuspid valve
TVRG=tricuspid regurgitant gradient

Introduction

1. General Introduction

Tricuspid valve regurgitation (TR) occurs in a variety of clinical settings. Historically, research was mainly focussed on left-sided heart disease. Therefore, TR and right heart disease have not been studied as extensively. However, in recent years, pathology of the right heart and tricuspid valve disease has gained more interest. Increasing TR severity and right heart dysfunction has been shown to impair prognosis in different heart disease.[1] Moreover, TR is often encountered in different heart disease, and has been shown to independently influence prognosis in patients with heart failure, congenital heart disease or pulmonary hypertension, and in patients undergoing resynchronisation therapy or implantation of a left ventricular assist device.[2-9] Furthermore, the impaired outcome after isolated tricuspid valve surgery remains incompletely understood.

Evaluation of the effect of TR is difficult because of its heterogenous presentation, and both its severity and prognosis is dependent on loading conditions. Therefore, in this thesis project, we evaluated the epidemiology, determinants and management of TR in selected patient populations.

2. Embryology and anatomy of the right heart

2.1 Embryology

The heart valves, supporting apparatus and cytoskeleton develop from the 5^{th} to 12^{th} week of embryogenesis, although the definitive trilaminar morphology of the leaflets further develops postnatally.

After formation and folding of the heart tube, endocardial cushions are formed at the level of the atrioventricular canal, located between the developing (left) atrium and the embryonic ventricle. **(Figure 1 a-d)** Four cushions are formed during embryonic development, namely the superior and inferior cushions, and the right and left lateral cushions. **(Figure 1d)** Extracellular matrix, called the cardiac jelly, is accumulated between the endocardium and the myocardium. This results in localized swellings. **(Figure 2a)** Next, a subset of endocardial cells delaminates from the myocardium and

transdifferentiates into mesenchymal cells by a process called epithelial-to-mesenchymal transformation (EMT). **(Figure 2a)** These cells proliferate and cellularize the endocardial cushions. In this rudimentary form, the cushions already prevent retrograde blood flow.[9] The atrioventricular canal expands, migrates rightwards and becomes funnel shaped, underlying the right and the left atrium.[10] **(Figure 1 c-f)** Furthermore, during atrial siltation by growth of the septum primum, the superior and inferior endocardial cushions fuse together. **(Figure 1 e-f)** The migration of the atrioventricular canal, the growth of the endocardial cushions and the atrial septation all lead to the separation of the atrioventricular canal into the mitral (left) and tricuspid (right) orifices and forms the inlet of the left and right ventricle respectively. **(Figure 1f)**

From the fused superior and inferior atrioventricular cushions arise the anterior mitral leaflet and the septal tricuspid leaflet. The left lateral atrioventricular cushion becomes the posterior mitral leaflet, whereas the right lateral cushion produces the anterior and posterior tricuspid leaflets.[11] The endocardial cushions elongate towards the ventricular cavity wall first along the atrioventricular canal myocardium and further down towards the ventricular myocardium. **(Figure 2 a-c)** As embryogenesis continues, the part overlying the atrioventricular canal myocardium gradually thins and elongates by a combination of apoptosis and cell proliferation, which results in further morphological changes towards the eventual valve leaflets.[12] Further down towards the ventricular cavity, the underlying ventricular myocardium separates and forms the papillary muscles, connected via the chordae tendinae and the developing leaflet.[11, 13] **(Figure 2c)** Although most of the formation of the valve leaflets is completed at 8 weeks of gestation, the adult trilaminar arrangement of the leaflets is only obtained after birth. The “fibrosa” at the ventricular side of the leaflet consists of densely packed collagen and the “atrialis” is located on the atrial side and consists mainly of elastic fibers. In between the fibrosa and the atrialis is a thin layer, rich in glycosaminoglycan and versican located, called the “spongiosa”.[14]

Around 7 weeks of gestation, formation of the fibrous annulus starts. The septal part of the annulus consists of the central fibrous body, the fused inferior and superior endocardial cushions and is continuous with the membranous ventricular septum.[15] On the other hand, from the free wall at the level of the atrioventricular groove, fibroadipose tissue grows towards the forming leaflets and further along the

atrioventricular sulcus towards the septal part of the annulus. The septal tricuspid leaflet and the anterior mitral leaflet are connected to each other through the septal part of the annulus and the central fibrous body. The annulus functions as a stable platform for the valvular complex and electrically isolates the atrium from the ventricle.

Figure 1 Schematic representation of the embryogenesis of the heart: Looping and septation of the heart.

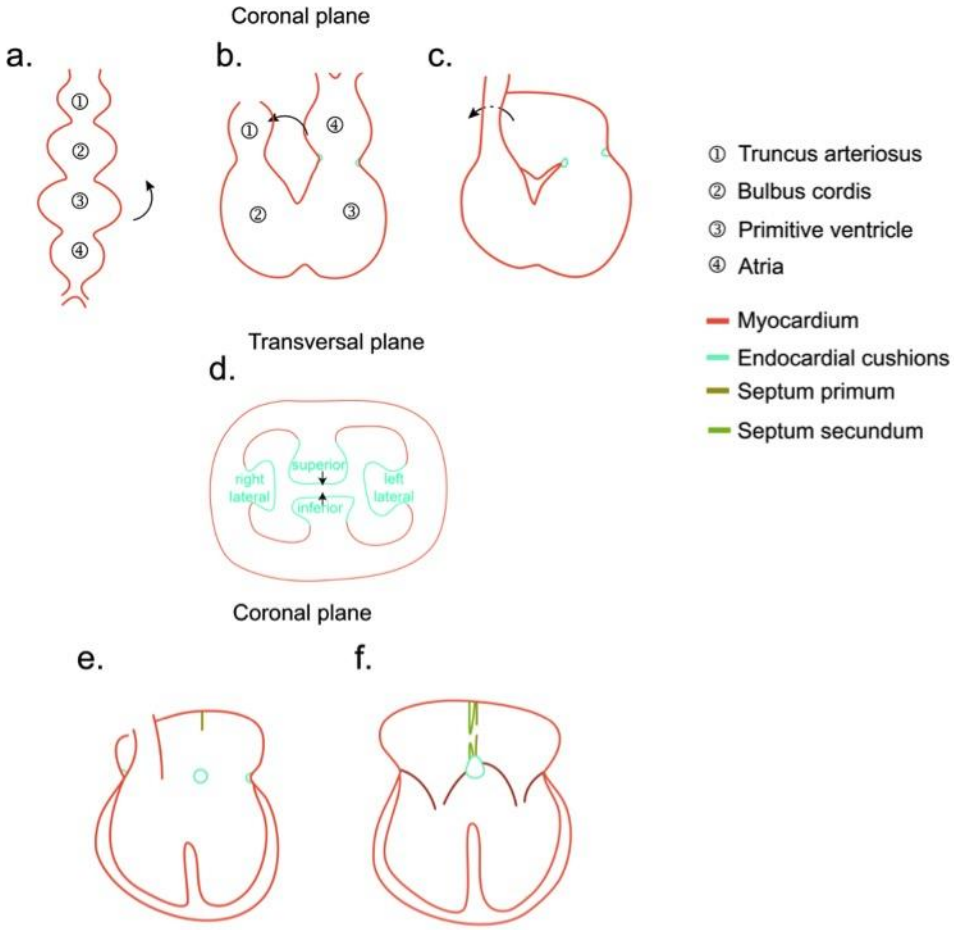
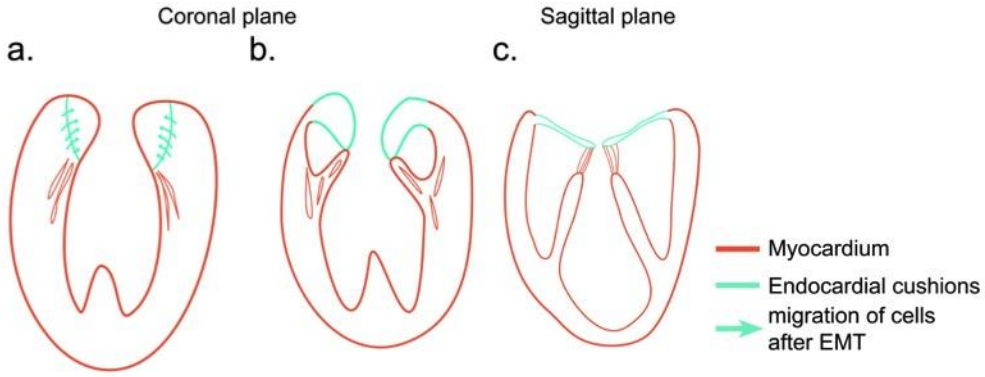


Figure 2 Formation of the heart valves: a. Migration of cells after epithelial-to-mesenchymal transdifferentiation to form the endocardial cushions; b. formation of rudimentary valve leaflets and septation of the ventricular myocardium to form the papillary muscles; c. Completion of the valvular complex consisting of valve leaflets, chordae tendinae and papillary muscles.



2.2 Anatomy

2.2.1 Valve structure

The tricuspid valve is located anteriorly in the chest, at the level of the right atrioventricular junction. It consists of 3 leaflets, a septal, posterior and anterior leaflet. **(Figure 3)** The anterior and posterior papillary muscles, and a less well-defined septal group of papillary muscles complete the valvular apparatus. However, this septal group of papillary muscles is an important part of the right ventricle as it separates the inflow part of the right ventricle from the infundibulum/outflow tract. **(Figure 4)** Furthermore, the septal chordal insertions play an important role in the development of tricuspid regurgitation in right ventricular dilatation. Multiple chordae originate from the papillary muscles and provide support for the 3 leaflets. Especially primary or edge chordae are important to preserve valvular competence whereas secondary chordae, which insert on the ventricular surface of the leaflet, are less essential for valvular function. It is easily possible to discriminate between the mitral valve and the tricuspid valve as the tricuspid valve has 3 leaflets, a lower insertion of the septal leaflet compared to the anterior mitral leaflet and chordal insertions are present on the ventricular septum. **(Figure 1f and Figure 3)**[16, 17]

Figure 3 Transthoracic echocardiographic image of the tricuspid valve in (A) end-diastole and (B) end-systole.

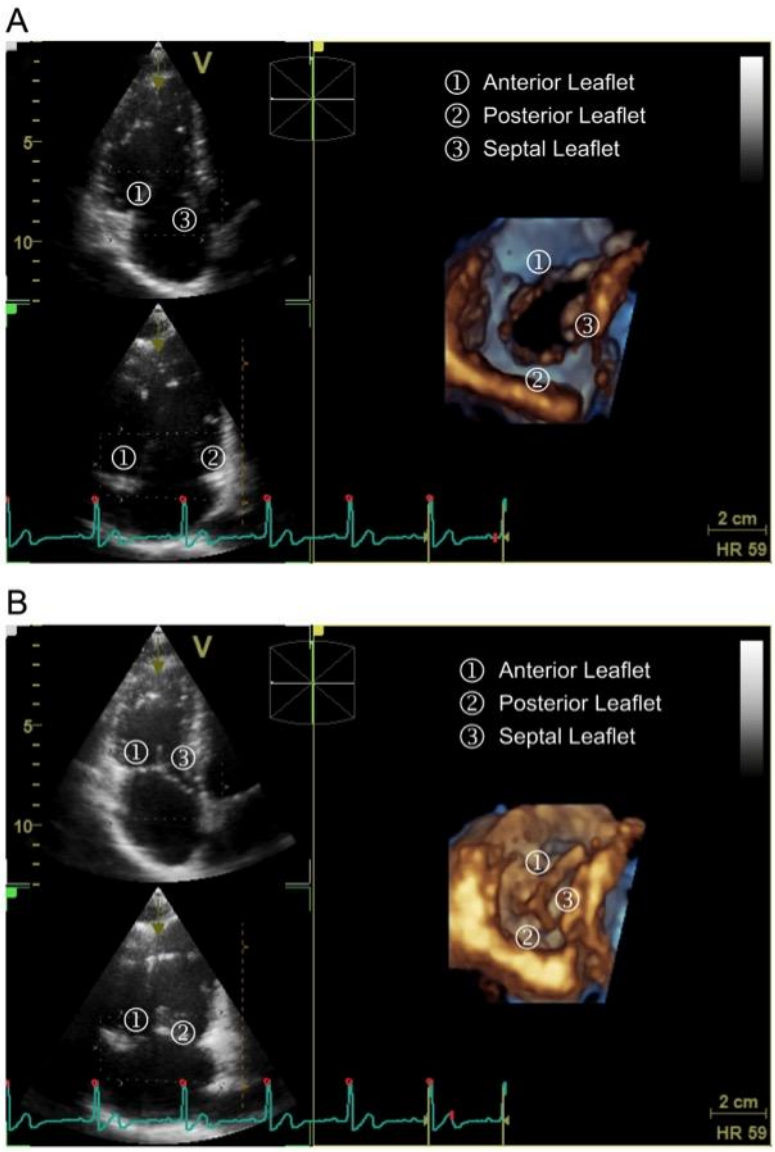
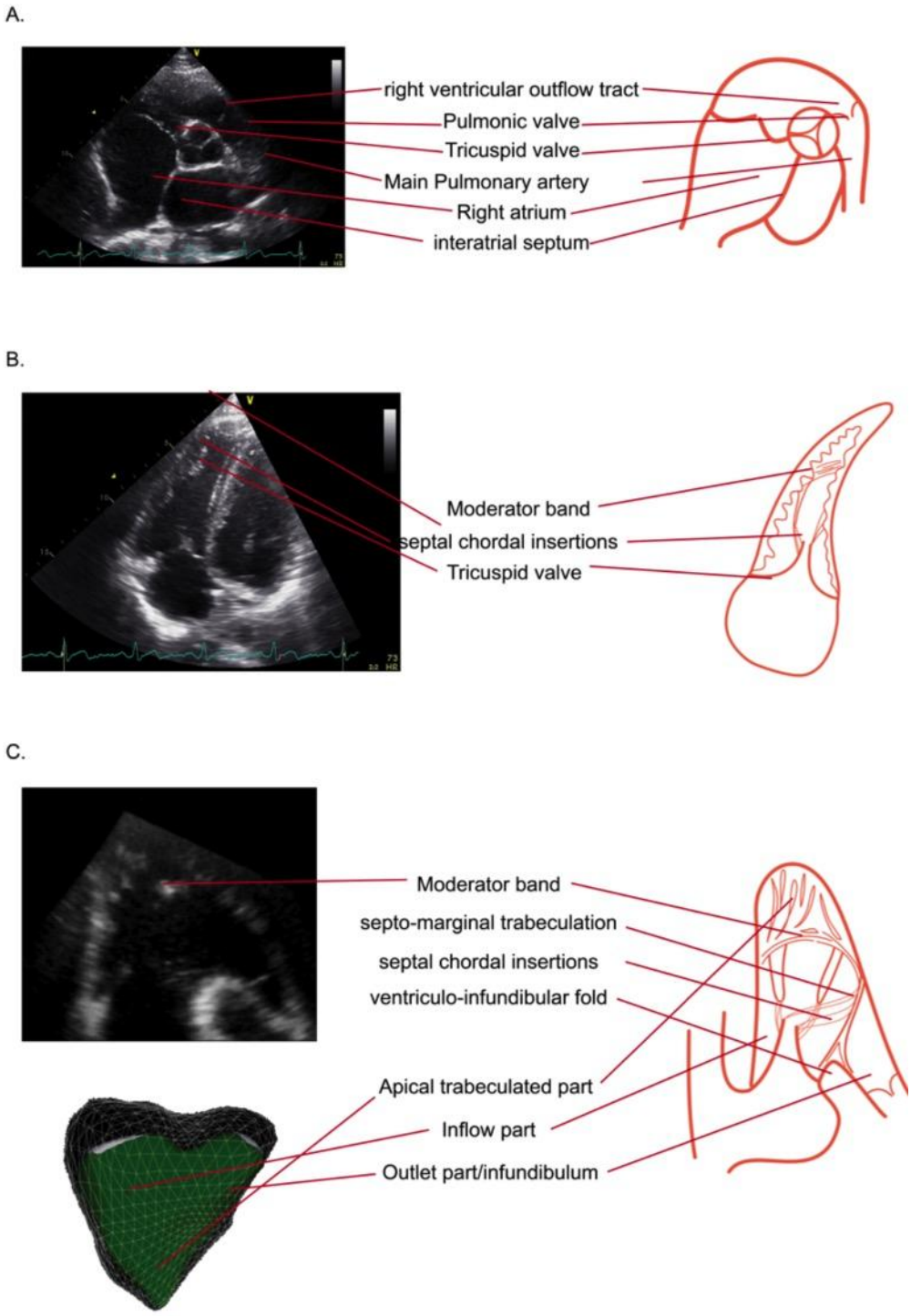


Figure 4 Right ventricular morphology and its relation with 2D transthoracic echocardiography (A-C) and 3D volume rendering in systole (green) and diastole (mesh) (C).



2.2.2 Cardiac cytoskeleton

The valve leaflets anchor on the cardiac cytoskeleton. The tricuspid annulus has a complex ellipsoid structure with 2 distinct high points (posteroseptal and anterolateral) and 2 low points, (anteroseptal and posterolateral). During a cardiac cycle, the tricuspid annulus is flatter at end-diastole and reaches its maximum height at end-systole. Furthermore, during cardiac contraction, the annular area shows a biphasic pattern with the area of the tricuspid annulus decreasing from late-diastole to mid-systole and during mid-diastole.[18, 19] Overall, the tricuspid annular area decreases 29.6 ± 5.5% during the cardiac cycle, which contributes to valvular competence.[20, 21]

2.2.3 The right ventricle

The right ventricle lies directly behind the sternum and has a complex 3-dimensional crescent shape, wrapped around the left ventricle. It consists of an inlet part, a trabeculated apical part, which contains the tension apparatus of the tricuspid valve, and a smooth but muscular outlet part. **(Figure 3)** The discriminator of the trabeculated apical part is the moderator band.[17] Compared to the left ventricle, which consists from 3 layers, the right ventricular wall is only composed of a superficial and deep muscle layer and lacks the middle, circumferential layer, responsible for the radial contraction of the left ventricle. The fibers of the superficial layer are arranged obliquely and continue into the superficial fibres of the left ventricle. This results in a close interrelation in contraction of both ventricles, known as ventricular interdependence. On the other hand, the deep muscle fibres are arranged longitudinally form base to apex. This myofibre orientation thus explains the contraction pattern of the normal right ventricle with a predominant longitudinal contraction, ejecting ±85% of the right ventricular volume.[22, 23]

2.2.4 Coronary circulation

The coronary blood supply of the heart consists of a left coronary artery, arising from the left sinus of valsalva, and a right coronary artery, arising from the right sinus of valsalva. The left coronary artery splits into the left anterior descending artery, following a course in the anterior interventricular groove providing blood to the anterior wall, the septal wall and the anterolateral wall of the ventricle. The circumflex artery runs around the heart in the left atrioventricular groove providing blood to the lateral wall. The right coronary artery runs along the right atrioventricular

groove and delivers blood to the right ventricular infundibulum (the conus branch), the sinus node and the atrioventricular node, and the right ventricular free wall. In 85% of individuals, the posterior descending artery arises from the right coronary artery, which travels along the posterior interventricular groove and provides blood to the inferior and posterior wall.

Noteworthy is that anomalous right ventricular blood supply occurs in fewer than 1 % of the normal population.[24, 25] In these patients it is important to identify if a coronary artery runs between the aortic valve/aorta and the pulmonary valve/pulmonary artery. This "malignant" course of the coronary arteries can impair coronary blood supply during exercise, which can lead to arrhythmias or sudden cardiac death.

3. Imaging the right ventricle and the tricuspid valve.

3.1 Evaluation of the right ventricle

The right ventricle consists of the inflow compartment, an apical part and the infundibulum. Moreover, the 3 compartments relate to each other in a complex 3-dimensional configuration. **(Figure 4)** This makes 2-dimensional imaging cumbersome as it is not possible to image all 3 compartments simultaneously. Two-dimensional echocardiography should therefore include different imaging planes to accurately visualize all parts of the right ventricle. Furthermore, the crescent shape in the frontal plane and the triangular shape of the ventricle in the sagittal plane explain why the geometric assumptions used to calculate left ventricular volume cannot be applied for volumetry of the right ventricle. Finally, endocardial border delineation is difficult because of the anterior position of the right ventricular free wall and because of the coarse trabeculations in the ventricle. **(Figure 4)**

The gold standard in evaluation of right ventricular morphology and function is cardiac magnetic resonance (CMR). It allows visualizing the right ventricle in the sagittal plane. The obtained slices can than be traced and combined to obtain a volume. The advent of 3D echocardiography offers an alternative to this. However, the volumes obtained by 3D echocardiography underestimate those obtained by CMR by 20-34%.[26] The most used echocardiographic measurement of right ventricular function is the tricuspid annular plane systolic excursion (TAPSE), obtained by M-mode imaging of the tricuspid annulus along the right ventricular free wall.

Calculation of right ventricular fractional area change from the apical 4-chamber view is more useful in patients with right ventricular dilatation. Myocardial performance index (MPI) represents a combination of isovolumic periods and ejection-time. However, isovolumic contraction and relaxation time are dependent on right ventricular systolic and diastolic function respectively, and of the loading conditions. Therefore, changes of the MPI don't necessarily point towards changes in ventricular function. Tissue Doppler velocity imaging can be used to evaluate the velocity of the tricuspid annulus during systole, as an alternative evaluation of longitudinal function of the right ventricle. Furthermore, strain and strain rate can be obtained by Tissue Doppler or by Speckle tracking imaging. This offers information of the myocardial deformation and velocities and offers an alternative approach in the assessment of right ventricular contractility. However, accurate tracking of the right ventricular free wall is challenging and the inter-vendor variability of the strain imaging packages makes that reference values are currently unavailable.

Lastly, one should take into account that all measurements are load-dependent. Because the right ventricle is prone to changes in loading conditions, indices of right ventricular function should always be interpreted with regards to right ventricular pressure- and/or volume-load.[27]

3.2 Evaluation of tricuspid regurgitation severity

In the assessment of tricuspid regurgitation, the cause, severity and impact on the right ventricular morphology and function should be evaluated. Quantification methods of TR are largely similar to those performed in mitral regurgitation. However, reference values are based on small studies and quantification methods are less robust.

First, leaflet abnormalities should be evaluated. Lower insertion of the septal leaflet in Ebstein's anomaly, or multiple TR jets in case of dysplastic valve leaflets point towards primary tricuspid valve disease. Likewise, thickening and calcification of valve leaflets should be reported. Three-dimensional echocardiography might be of use in the evaluation of tricuspid valve leaflets.[28] Secondary TR, with normal leaflets, most often presents with a single regurgitant jet, annular dilation and increased an tricuspid regurgitant velocity.[29]

Initial evaluation of the severity of TR is performed by Colour Doppler flow.

Dependent on the area of the regurgitant jet, patients can be classified as having mild (1/4) to severe TR (4/4). Although associated with several caveats, this measurement is still readily used in clinical practice as it presents an easy and quick way to grade TR. However, when more than moderate TR is suspected, these measurements should be supplemented with more semi-quantitative and quantitative measurements. A vena contracta width > 7 mm (at Nyquist limit of 50-60 cm/sec), a proximal isovelocity surface area (PISA) radius of >9 mm (at baseline Nyquist limit shifted down to 28 cm/sec), a calculated EROA of ≥ 40 mm2 and a regurgitant volume of ≥ 45 mL are indicative for severe TR. Furthermore, indirect signs of severe TR are systolic flow reversal in the hepatic veins, significant dilatation of the inferior vena cava or signs of volume-loading of the right ventricle are additive to the grading of TR severity.[30]

Lastly, the effect of TR on RV morphology and function should be assessed. Significant volume-loading results in right ventricular dilation, right atrial dilatation, RV eccentricity index > 2 at end-systole and signs of right ventricular dysfunction can help identify patients eligible for surgery.[31-33]

4. Origin of tricuspid valve regurgitation

In reference to the complex anatomy of the right ventricle and the tricuspid valvular complex, valvular incompetence originates from (1) changes in morphology of the tricuspid leaflets, both congenital and acquired; (2) tricuspid annular dilatation; (3) changes in right ventricular geometry and (4) right ventricular function, the latter closely related to left ventricular function.

Tricuspid valve regurgitation is divided into 2 types: (a) primary and (b) secondary or functional tricuspid valve regurgitation.

4.1 Primary tricuspid valve regurgitation

In only 10-20% of patients, tricuspid regurgitation is due to primary disease of the tricuspid leaflets.[34-36] Common causes of primary tricuspid valve regurgitation are rheumatic heart disease, myxomatous heart disease, Ebstein's anomaly, endomyocardial fibrosis, endocarditis, carcinoid disease or traumatic (blunt chest injury, laceration).

4.2 Secondary tricuspid valve regurgitation

Tricuspid valve regurgitation is secondary in 80-90% of cases. In these patients, tricuspid valve leaflets morphology is normal and TR originates from left heart disease (LV dysfunction or valve disease) resulting in pulmonary hypertension, any cause of increased right ventricular pressure (chronic lung disease, pulmonary thromboembolism, left to right shunt) or any cause of right ventricular dysfunction (myocardial disease, RV ischemia or infarction).[34, 35]

The pathogenesis is mainly attributable to changes in morphology of the right heart (tricuspid annular dilatation, right ventricular dilatation due to left heart failure (myocardial or valvular causes), right ventricular volume-overload (e.g. atrial septal defect)) or right ventricular pressure-load. Furthermore, the presence of atrial fibrillation has shown to be associated with increased tricuspid regurgitation. Lastly, tricuspid valve regurgitation itself causes a volume-overload of the right ventricle, causing further dilatation of the right ventricle and tricuspid annulus, resulting in more severe tricuspid valve regurgitation.[20, 31, 37-40] **(Figure 5)**

However, each geometric or hemodynamic change in right heart morphology is not necessarily associated with severe tricuspid regurgitation. In tricuspid regurgitation, the tricuspid annulus looses its 3-dimensional shape and becomes more planar.[19] In vitro studies have shown that an increase of the annular circumference by 40% leads to severe TR.[38] Conversely, patient data show that annular dilatation does not invariably lead to severe TR. Sadeghi et al studied patients with chronic thromboembolic pulmonary hypertension after pulmonary endarterectomise. Although the circumference of the tricuspid annulus remained equal, great differences in persistence of TR could be seen after surgery, mainly attributed to the success of lowering the right ventricular pressure load.[41]

Inducing acute increases in pressure-load by infusing Methoxamine in a pig-model causes an increase in tricuspid regurgitation severity.[42] However, in patients with pulmonary hypertension, all degrees of severity of tricuspid regurgitation are encountered.[39]

Furthermore, the geometry of the right ventricle is of the utmost importance in the pathogenesis of tricuspid regurgitation. The insertion of the chordae and the placement of the papillary muscles make the valvular complex very prone to

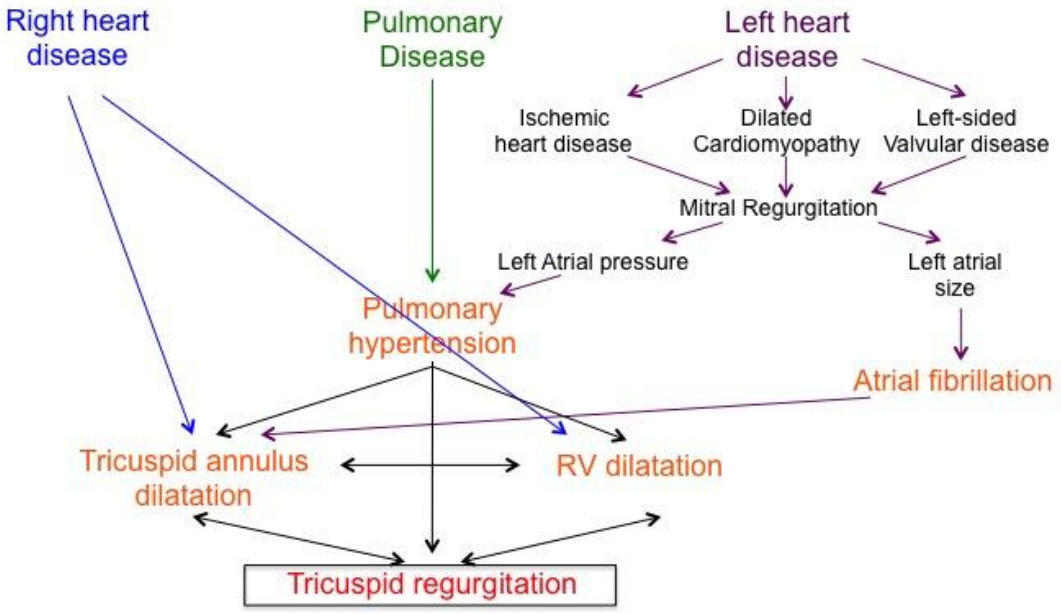
geometric changes of the right ventricle. Dilatation occurs mainly along the right ventricular free wall, which results into a displacement of all papillary muscles from the centre of the ventricle and annular dilatation.[38] Fukuda et al. confirmed that tenting area and tenting height were predictive of the result of tricuspid annuloplasty, confirming the importance of right ventricular geometry and papillary muscle placement in these patients.[43]

The above indicates the complex interplay of the different determinants of tricuspid regurgitation and indicates the difficulty in assessing the tricuspid valve pre-operatively and predicting outcome after surgery.

4.3 Iatrogenic tricuspid valve regurgitation

TR can also occur after repetitive RV biopsies for instance in patients after heart transplantation or after placement of a pacemaker or defibrillator lead.

Figure 5 Pathogenesis of functional tricuspid regurgitation. (Adapted from Shoran et al. J Am Coll Cardiol 2009;53(5):401-8)



5. Epidemiology

Any severity of TR is present in 79.5-85.9% of people in the general population. Low severity TR is frequent and has long been regarded as a chance finding.[44] Some authors even suggested mild TR to be an artefact of the movement of the tricuspid valve leaflets.[45] On the other hand the prevalence of significant TR, defined as TR > 2/4, was found to be 1.2 to 5.6% in the general population. Furthermore, the prevalence of TR is age-dependent and ranges from 0.9% in people younger than 50 years to 5.6% in people over 70 years of age.[44, 46]

Functional TR has long been regarded as a consequence of the underlying, often left-sided heart disease. More specifically, in mitral valve disease it was thought TR would resolve after surgery of the mitral valve, as this would remove the cause of right ventricular hypertension.[47, 48] In recent years, it has become clear that TR is not simply a bystander phenomenon. In the general population, increasing severity of TR has been shown to have an impact on prognosis.[1] Moreover, TR is often encountered in different heart disease, and has been shown to independently influence prognosis in patients with heart failure, congenital heart disease or pulmonary hypertension, and in patients undergoing resynchronisation therapy or implantation of a left ventricular assist device.[2-8]

This indicates that the development of TR should alert the clinician for possible disease progression and indicates patients at higher risk for mortality. However, although TR is associated with worse prognosis, the reason for this remains unclear.

6. Studied populations

In this thesis, we first evaluated the prevalence and determinants of TR in the population referred for echocardiography. Next, we selected 4 patient populations, in whom excessive pressure or volume load of the right ventricle was present for further study.

6.1 Pulmonary valve stenosis

The incidence of patients with pulmonary valve stenosis is 1 in 2000 live births and it accounts for 8% of all congenital heart defects. Stenosis occurs due to absent separation of the valve leaflets, resulting in a dome-shaped valve with a pinpoint

orifice. In 10-20% of patients, the stenosis occurs due to thickening of the valve leaflets with commissural fusion or is caused by pulmonary valve dysplasia. The latter valvular abnormalities are often part of a collection of clinical signs associated with a specific syndrome.[49-51]

In the clinical work-up, Doppler echocardiography is the evaluation tool of choice. A transvalvular gradient of <36 mmHg, between 36-64 mmHg and >64 mmHg is considered as mild, moderate and severe pulmonary valve stenosis respectively.[52] Severe pulmonary valve stenosis impairs functional capacity, and valvular dilatation, valve repair or valve replacement is often indicated. On the other hand, mild pulmonary valve stenosis seldomly progresses after adolescence and is considered benign.[51, 53]

6.2 Tetralogy of Fallot

The incidence of patients with "Tetralogy of Fallot" is estimated around 1/3000 to 1/1500 life births. It is the most common cyanotic congenital heart disease and accounts for approximately 10% of all congenital heart defects. It consists of a combination of 4 defects: (1) a non-restrictive ventricular septal defect; (2) an overriding aorta; (3) right ventricular outflow tract obstruction at the level of the infundibulum, the pulmonary valve, postvalvular, at the level of the pulmonary arteries or a combination and (4) right ventricular hypertrophy. In approximately 15 % of patients, tetralogy of Fallot occurs as part of a deletion of chromosome 22q11, which results into the "DiGeorge Syndrome" (CATCH22).[54, 55]

Patients with tetralogy of Fallot are often recognized early, as significant outflow tract obstruction results in right-to-left shunting through the ventricle septum defect, which results in cyanosis. Rarely, outflow tract stenosis is mild, with hemodynamics comparable to patients with an isolated ventricle septum defect, the so-called "pink Fallot".

Patients undergo surgery at young age, sometimes as a staged approach to increase blood flow to the pulmonary circulation allowing the pulmonary vasculature to mature. Eventually, and nowadays in infancy, a complete correction with closure of the ventricle septum defect and relieve of the outflow tract obstruction, sometimes with a pulmonary homograft.

From a morphological point of view, 2 elements especially warrant close follow-up: (1) outflow tract function (stenosis and regurgitation) and (2) right ventricular function. Furthermore, left ventricular dysfunction, aortic regurgitation and root dilatation, endocarditis, arrhythmias (supraventricular and ventricular) and sudden cardiac death are late complications after complete repair.[56, 57]

6.3 Pulmonary hypertension

Pulmonary hypertension can be seen in multiple clinical conditions. It is diagnosed by right heart catheterisation and is defined as a mean pulmonary artery pressure ≥ 25 mmHg and a pulmonary capillary wedge ≤ 15 mmHg (pre-capillary pulmonary hypertension) or pulmonary capillary wedge ≥ 15 mmHg (post-capillary pulmonary hypertension). At the moment of the study, patients with PH were classified according to the Dana Point classification into 5 groups according to the cause of the elevated pulmonary pressures: Group 1: pulmonary arterial hypertension (PAH); Group 2: pulmonary hypertension due to left heart disease; Group 3: pulmonary hypertension due to lung disease; Group 4: chronic thromboembolic pulmonary hypertension and Group 5 consists of patients with an unclear or multifactorial mechanism resulting in elevated pulmonary pressures.[58, 59] Recently, a new classification has been proposed.[60]

Although the availability of pulmonary-specific therapy has significantly improved outcome in patients with PAH, mortality and functional impairment remains high.[61, 62] Furthermore, pulmonary endarterectomy (PEA) effectively reduces right ventricular afterload. Although the right ventricle can successfully adapt to the progressive and chronic pressure-load by hypertrophy of the right ventricular myocardium, eventually right ventricular failure occurs. Although therapy successfully reduces pulmonary vascular resistance, lowering the load on the right ventricle, progressive right ventricular dysfunction may occur. This decrease in right ventricular function is closely associated with worse outcome.[63]

6.4 Atrial septum defect type secundum

Atrium septum defect type secundum occurs in approximately 1/1000 live births, consists of 70% of all atrium septum defects. As an isolated lesion, it accounts for 6-10% of all congenital heart lesions. It originates from excessive reabsorption of the septum primum.[54, 64, 65]

After birth, as pulmonary vascular resistance is diminished, a predominantly left-to-right shunt occurs which exposes the right ventricle to an increased volume-load. This results in right ventricular dilatation, tricuspid valve regurgitation and increased pulmonary pressures due to high pulmonary flow. If the atrial septal defect is closed early in life, patients have a survival equal to the general population.[66, 67] Although the closure of an atrial septum defect at older age has been subject of debate, several studies have indicated closure results in decreased mortality and morbidity, and remodelling of the right heart chambers occurs.[68, 69] However, if closed later in life, a lesser decline in pulmonary vascular resistance during exercise is observed. This results in higher pulmonary pressures relative to the cardiac output developed by the patients during exercise.[70]

7. Right ventricular function and hemodynamic consequences of volume- and/or pressure-load.

Right ventricular contraction is dependent on loading conditions.[23] The right ventricle arrives at developing similar cardiac output, only at one fifth of the energy cost needed for left ventricular contraction. The pressure-volume curve of the normal right ventricle differs from the left ventricle in different aspects. In the right ventricle, a time difference between the pulmonary arterial dicrotic notch and peak right ventricular pressure can be noted, the so-called hangout period.[71, 72] The pulmonary valve closes only when a significant decrease in right ventricular pressure has already occurred. Hence, when plotting the pressure-volume loop of the right ventricle, there is no clearly defined isovolumic relaxation time and the curve has a more triangular shape as compared to the square curve of the left ventricular P-V loop.[73]

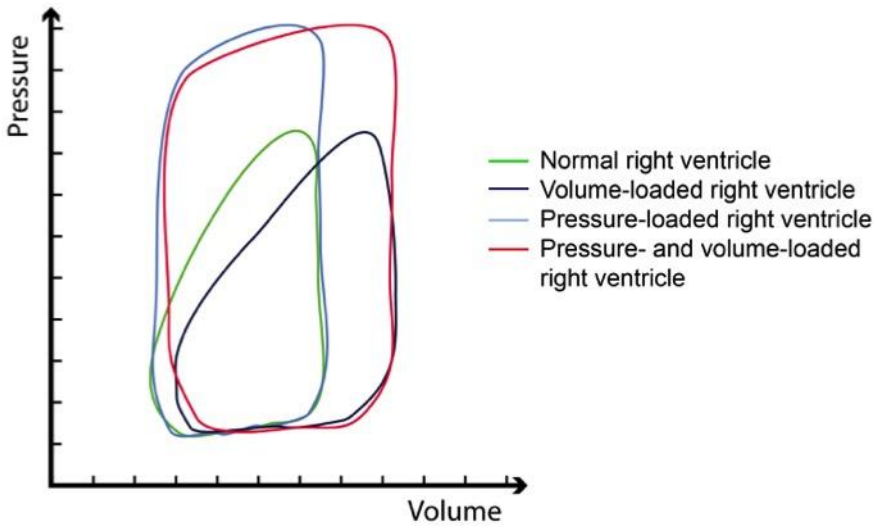
This contraction pattern is mainly related to the low impedance of pulmonary vascular bed more then an intrinsic myocardial property, as a sub-pulmonary left ventricle assumes a comparable pattern. Vice versa, a systemic right ventricle assumes a contraction pattern comparable to that of the normal left ventricle.

Acute changes in afterload of the right ventricle, even small, have already an important impact on right ventricular contractile performance and stroke volume. Small (acute) increases in afterload can be seen during respiration.[74] At the other end

of the spectrum, acute pulmonary emboli cause a large and acute increase of right ventricular afterload severely impairing right ventricular function.

Changes in loading conditions of the right ventricle, result in different changes of the pressure-volume load.**(Figure 6)**

Figure 6 Impact of pressure and/or volume-load on the right ventricular pressure-volume relationship.



The right ventricle tolerates an increased volume-load fairly well. The major changes in the pressure-volume plot are an increase in end-diastolic and, to a lesser extent of the end-systolic volume. This results in an increased stroke work. The right ventricle, with its thin wall and longitudinally oriented myocardial fibers, is well suited to support this additional volume-load.[75, 76]

When a pressure-load is imposed on the right ventricle, the pressure-volume loop changes and closely resembles the loop of the left ventricle. This means end systolic pressures are more elevated, when well tolerated, with similar end-diastolic and end-systolic volumes. Importantly, distinct isovolumic periods can be identified. Furthermore, the stroke work is increased. Studies have shown that this pressure-load is initially well tolerated, but fast deterioration of right ventricular function occurs. The right ventricle dilates, becomes more spherical and hypertrophies, which also results in impaired blood supply to the myocardial wall.[77]

The combination of pressure and volume-load results in increase in right ventricular end-diastolic and end-systolic volumes, in combination with increased end-systolic pressure and a further increase of stroke work, delivered by the ventricle. At least from theoretical point-of-view, this represents considerable strain on the right ventricle and could lead to quick deterioration of right ventricular function.

The blood supply to the right ventricular free wall is dependent on a single coronary vessel, which makes it more vulnerable to coronary artery disease, especially in patients with a systemic right ventricle. Furthermore, in case of increased wall stress due to either volume- or pressure-load on the right ventricle, blood flow through the right coronary artery is limited or absent throughout systole. This impairs blood supply and can cause ischemia of the right ventricular wall. This results in endomyocardial fibrosis, and can lead towards impaired right ventricular contractile function.[78, 79]

8. Prediction of pulmonary hypertension

Pulmonary hypertension is associated with different heart disease and is associated with morbidity and mortality.[61, 80] More specifically in pulmonary arterial hypertension, current evidence points towards improved prognosis if diagnosis is made early.[81-83] In patients susceptible for development of pulmonary hypertension, echocardiographic determination of the tricuspid regurgitant velocity is advised as initial screening.[58]

In an attempt to develop screening algorithms and prediction methods for pulmonary hypertension, symptoms, echocardiography, lung function tests and biomarkers are often used. With these data, a risk score is developed by regression analysis.[84] It is important to emphasize that these algorithms and scores are only applicable to the studied population and the prevalence of the disease in the studied cohort has to be comparable to that of the population that will be screened. Many of the prediction algorithms and scores are focused on the early detection of PH in specific patient populations, such as in systemic sclerosis.[85, 86] The prediction scores can therefore only be used in these patient populations. Furthermore, referring to Bayes theorem, predictive values will vary greatly if prevalence in the screened population is different from the studied population.

Doppler derived tricuspid regurgitant velocities in the individual patients are sometimes difficult to obtain. The measurement can only be acquired in 75-90% of patients in experienced hands and even then suboptimal CW traces are often obtained.[87, 88] Therefore, a simple echocardiographic technique to exclude pulmonary hypertension might be interesting.

9. Management of tricuspid valve regurgitation

Medical treatment of severe tricuspid regurgitation is limited to the use of loop diuretics and aldosterone blockers. However, decreasing afterload by specific pulmonary vasodilators has shown to improve right ventricular function and decrease tricuspid regurgitation in the post-operative setting and might be an alternative, although experience is very limited.[58, 89, 90]

Often, the only successful treatment for tricuspid regurgitation is surgery. In the evaluation of patients for surgery, 2 distinct scenarios can be identified: (1) tricuspid valve repair at the time of left-sided valvular surgery and (2) Isolated tricuspid valve repair. The current recommendations of the European society of cardiology are listed in **Table 1.**[33] These largely agree with the more recently published guidelines of the American Heart Association and the American College of Cardiology.[32]

9.1 Tricuspid valve regurgitation in mitral valve disease

Mitral regurgitation is often associated with tricuspid regurgitation. Furthermore, TR progression towards moderate and severe TR occurs in up to 30% of patients undergoing isolated mitral valve surgery and can even occur 10 years after the initial surgery. Late occurrence of tricuspid regurgitation is known to be associated with worse prognosis.[91-95] Left-sided valvular surgery offers a unique opportunity to prevent further deterioration of tricuspid valve function. Key factors, associated with an increased prevalence of tricuspid regurgitation progression after surgery are annulus dilatation, right ventricular dysfunction, tricuspid leaflet tethering, pulmonary hypertension, atrial fibrillation, non-myxomateous aetiology of mitral regurgitation and the presence of a transvalvular pacemaker.[95-97] However, even then, the natural history is unpredictable. Although reduction of tricuspid regurgitation severity has been observed after pulmonary endarterectomy and mitral valve surgery, progression of TR is observed after mitral valve repair in ischemic cardiomyopathy, dilated

cardiomyopathy and in rheumatic heart disease.[41, 47, 98-101] Therefore, some authors even argue in favour of "prophylactic" tricuspid annuloplasty at the time of left-sided heart surgery.[102]

Table 1 Indication for surgery in patients with tricuspid valve regurgitation. (Vahanian et al. Eur Heart J 2012;33(20):2569-619)

	Class	**Level**
At the time of left-sided valve surgery:		
Surgery is indicated in patients with severe primary or secondary TR undergoing left-sided valve surgery	**I**	**C**
Surgery should be considered in patients with moderate primary TR undergoing left-sided valve surgery.	**IIa**	**C**
Surgery should be considered inpatients with mild or moderate secondary TR with dilated annulus (≥40 mm or >21 mm/m2) undergoing left-sided valve surgery	**IIa**	**C**
In isolated tricuspid regurgitation		
Surgery is indicated in symptomatic patients with severe isolated primary TR without severe right ventricular dysfunction.	**I**	**C**
Surgery should be considered in asymptomatic or mildly symptomatic patients with severe isolated primary TR and progressive right ventricular dilatation or deterioration of right ventricular function	**IIa**	**C**
After left-sided valve surgery, surgery should be considered in patients with severe TR who are symptomatic or have progressive right ventricular dilatation/dysfunction, *in the absence* of left-sided valve dysfunction, severe right or left ventricular dysfunction, and severe pulmonary vascular disease.	**IIa**	**C**

However, it is important to emphasize that the true clinical benefit of tricuspid annuloplasty in the setting of mitral valve disease has not been proven. On the other hand, several studies have shown favourable remodelling after concomitant tricuspid surgery as well as improved functional capacity.[103-105]

9.2 Isolated tricuspid valve regurgitation

The surgical indication in patients with isolated tricuspid regurgitation is not well established. Furthermore, clinicians are reluctant towards isolated tricuspid valve surgery, as this historically is associated with a high post-operative mortality. At present, only symptomatic patients with severe tricuspid regurgitation have a strong indication for surgery. Furthermore, progressive right ventricular dysfunction and right ventricular dilatation in follow-up echocardiography is seen as an indication to refer patients towards surgery. However, this advice is mainly based on small studies performed in patients with carcinoid disease and in patients with flail leaflets or are based on studies in patients with mitral valve regurgitation.[106, 107] The heterogeneity of patients presenting with isolated tricuspid regurgitation makes generalisation of these guidelines difficult.

9.3 Tricuspid valve surgery after left-sided valve surgery

Lastly, a specific patient population are those patients referred for severe tricuspid regurgitation after mitral valve surgery. Especially in this patient population, high post-operative mortality is observed after isolated tricuspid valve surgery.[108-111] Referral for patients with severe tricuspid regurgitation after mitral valve regurgitation is most often late, after significant right ventricular dilatation and dysfunction is already present.[111-113]

10. Choice of surgical intervention

Controversy still exists concerning which procedure should be performed when performing tricuspid valve surgery. Surgery of the tricuspid valve should focus on the annulus, the commissures, the leaflets morphology and the tethering of the leaflets. In many patients, the morphology of the valve leaflets is normal, and tricuspid regurgitation is mainly a result of increased annular dimensions. In these patients *tricuspid annuloplasty* can be performed, with or without insertion of a *ring*. If

leaflets are slightly damaged, the surgeon can choose to *repair* the valve. Leaflet tethering is sometimes relieved by leaflet augmentation, increasing the amount of valve tissue resulting in better coaptation of the valve leaflets.[114]

On the other hand, when the tricuspid leaflets or the right ventricle is importantly damaged, *tricuspid valve replacement* has to be performed. Current guidelines favour tricuspid valve repair because of the better post-operative outcome compared to patients undergoing valve replacement.[32, 33] However, it is clear that patients undergoing tricuspid valve replacement present in a worse clinical state and often have a more severely damaged tricuspid valve. [115] Even more so, if corrected for co-morbidities, outcome of tricuspid valve replacement is similar compared to patients undergoing tricuspid valve repair and is associated with lower degrees of tricuspid valve regurgitation post-operatively and in in long-term follow-up.[116, 117] Likewise, the choice to implant a mechanical or biological tricuspid valve is subject of discussion. No difference in post-operative outcome and overall survival rates is observed in patients either receiving a mechanical or a biological tricuspid valve replacement, even in younger patients.[118-121] More thrombosis, embolism and bleeding occurred in the group receiving a mechanical tricuspid valve replacement compared to patients who received a biological tricuspid valve, even though both patient groups received oral anticoagulation therapy. On the other hand, a higher rate of bioprosthetic degeneration can be observed.[121]

Aims of the study

1) Epidemiology and prevalence tricuspid regurgitation in patients referred for echocardiographic evaluation and in different heart disease.
2) Evaluation of the determinants of tricuspid regurgitation severity and applicability in clinical practice.
3) Changes in tricuspid regurgitation and right ventricular function in the setting of acute afterload increase by exercise.
    a. After closure of atrial septum type secundum.
    b. In patients with mild to moderate pulmonary valve stenosis.
    c. In patients with repaired tetralogy of Fallot.
4) Evaluation of surgical management of tricuspid regurgitation.
    a. In patients with isolated tricuspid regurgitation
    b. In the setting of mitral valve surgery.

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Chapter 1

Tricuspid valve regurgitation: prevalence and relationship with different types of heart disease.

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Abstract

Objectives

The clinical impact of tricuspid valve regurgitation (TR) is in most cases undetermined. This study aimed at evaluating: (1) the prevalence of tricuspid valve regurgitation, (2) the degree of its relationship with several types of heart disease and (3) the association of the routine echocardiographic variables with TR in each cardiac pathology.

Methods and results

The database of the University Hospitals of Leuven was searched for all transthoracic echocardiographic studies, performed between November 2010 and January 2011, to reach a target of at least 2000 patients. The study population was divided into predefined categories of heart disease: cardiac hypertrophy, heart transplantation, ischaemic cardiomyopathy, non-ischaemic cardiomyopathy, valvular heart disease and pulmonary hypertension. Furthermore a subgroup with a structurally normal heart was identified. Significant TR was defined as graded > 2/4 on colour Doppler. In total 2054 consecutive echocardiographic studies were retrieved. The prevalence of significant TR was 10.2% in the total population, ranging from 1.1% to 34.4%. Compared to patients with a structurally normal heart, TR was strongly associated with pulmonary arterial hypertension (PAH)[OR 35.8 (11.7-110.3; P < 0.001)], valvular heart disease [OR 6.7 (2.3-19.2; P < 0.001)], heart transplantation [OR 10.4 (3.4-31.8; P < 0.001)], non-ischaemic cardiomyopathy [OR 6.2 (1.8-21.3; P = 0.004)], and ischaemic cardiomyopathy [OR 5.6 (1.5-21.8; P = 0.012)]. TR was significantly related to the degree of mitral valve regurgitation (MR) in all categories (P < 0.001).

Conclusion

TR occurs frequently and is in a different degree related to the underlying heart disease. TR was also associated to MR. This might suggest valvular interdependence between the tricuspid and mitral valves.

Introduction

Tricuspid valve regurgitation (TR) is a common finding on routine echocardiography.

TR of any severity is detected in up to 85.7% of echocardiographic examinations.[1] The prevalence of moderate to severe TR varies in patients between 1.5% and 15% and is age-related.[1,2]

The anatomy of the tricuspid valve and its subvalvular apparatus is complex. It consists of a fibrous tricuspid annulus, three leaflets (anterior, posterior and septal), two well-defined papillary muscles (anterior and medial) and one septal group of papillary muscles. The papillary muscles provide chordae to the tricuspid leaflets. Accessory chordal attachments to the right ventricular free wall and to the moderator band are present as well.[3,4]

TR is most often functional, caused by tricuspid annular dilation that changes its three-dimensional geometry, and is frequently a consequence of left-sided heart failure.[5,6] Primary (structural) TR accounts for 8-10% of all TR.[2,7] Finally, iatrogenic causes such as a transvenous right ventricular pacing or shock lead, and repetitive right ventricular myocardial biopsies may induce significant TR.[8,9]

TR has also an impact on the physical capacity. Patients who underwent successful mitral valve surgery, however, without simultaneous tricuspid valve annuloplasty, had a lower NYHA functional class and exercise capacity when compared to patients who underwent tricuspid valve annuloplasty.[10,11] Increasing severity of TR is also associated with progression of symptoms, heart failure, and even death.[10,12,13] Despite these findings, guidelines do not advise early intervention on the tricuspid valve, probably because isolated tricuspid valve surgery is considered a high-risk procedure with a perioperative mortality as high as 50% in some older series, but actually estimated between 8.8 and 25%.[14-21]

To avoid ignoring TR, this study aimed at evaluating: (1) the prevalence of tricuspid valve regurgitation, (2) the degree of its relationship with several types of heart disease and (3) the association of the routine echocardiographic variables with TR in each cardiac pathology

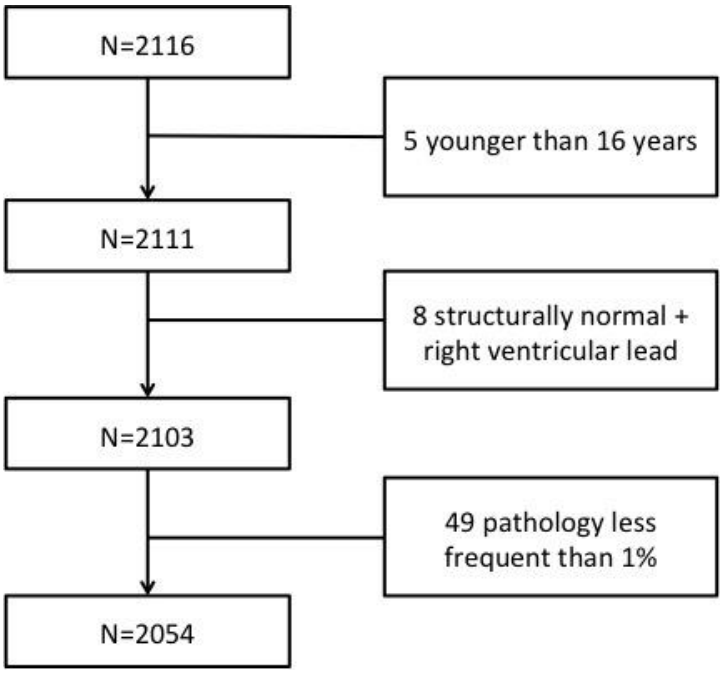
Methods

Patient selection and data collection

Patients were identified throughout the database of cardiac imaging at our institution,

a tertiary care centre. The database consists of hospitalized patients, referrals from the outpatient clinics as well as externally referred patients. The data of all consecutive routine transthoracic echocardiographic examinations, performed between November 2010 and January 2011, were exported to a separate database for statistical analysis. The target was to achieve a total of at least 2000 echocardiographic examinations of different patients. When patients underwent more than one examination in this time period, the first available examination was used for inclusion in the study. Patients under age 16, patients with complex congenital defects, and patients with a structurally normal heart but a transvenous lead were excluded (figure 1). The local ethics committee approved the selection and the review process.

Figure 1 Number of patients excluded from analysis



Echocardiographic studies

Experienced staff, supervised by a senior cardiologist, performed all echocardiographic studies. Measurements where done according to the criteria of the American Society of Echocardiography.[22]

Left ventricular function was evaluated by means of a combination of visual

assessment and echocardiographic measurements and is represented by the left ventricular ejection fraction (LVEF, %). A LVEF ≤ 50% was considered as ventricular systolic dysfunction. Left ventricular dilation was defined as an end-diastolic diameter larger than 53 mm. Left ventricular cardiac output was determined based on the continuity equation. The right ventricle was termed dilated when the maximal end-diastolic diameter exceeded 33 mm. The right and left atrial dimensions were determined at end systole. Valvular regurgitation severity was graded on a scale of 0 (no regurgitation) to a maximum score of 4, based on semi-quantitative colour Doppler flow mapping in all possible incidences with a jet-to-atrial-area ratio below 10% (grade 1), from 10 to 20% (grade 2), from 20 to 40% (grade 3) and above 40% (grade 4). Aortic valvular stenosis was evaluated by determining the pressure gradient across the valve using continuous wave (CW) Doppler echocardiography and the end-systolic aortic valve area (AVA) using the continuity equation. The severity of the valve lesion was defined as follows: no stenosis, elevated pressure gradient (CW Doppler derived peak pressure gradient > 12 mmHg), mild (CW Doppler derived peak pressure gradient > 20 mmHg), moderate (AVA ≥ 1 cm2 and CW Doppler derived peak pressure gradient > 80 mmHg or mean pressure gradient < 50 mmHg) and severe aortic stenosis (AVA < 1 cm2). Pulmonary artery systolic pressure (PASP) was estimated by CW Doppler echocardiographic measurement of peak regurgitant systolic velocity, using the simplified Bernoulli equation (4*TR velocity^2). Right atrial pressure was not taken into account. A specific cut-off value for elevated PASP has not been defined in the literature. A value of ≥ 40 mmHg (TR velocity ≥ 3.2 m/sec) was used as the cut-off for elevated PASP to avoid overestimating the prevalence of pulmonary hypertension. Dilation of the inferior vena cava was noted if the diameter was larger than 20 mm at inspiration and in absence of normal respiratory variation.

Predefined categories of heart disease

Patients were divided into 9 groups: (1) structurally normal heart, (2) cardiac hypertrophy, (3) coronary artery disease (CAD), (4) ischaemic cardiomyopathy (CMP), (5) non-ischaemic CMP, (6) valvular heart disease, (7) pulmonary arterial hypertension (PAH), (8) heart transplant, and (9) oncologic pathology. When a patient could be allocated to more than one group, the main reason of follow-up or the reason for referral was the first criterion for assignment to one specific category. Next,

echocardiographic structural abnormalities were considered more important than non-structural abnormalities in the allocation process.

The **"structurally normal heart"** refers to patients who were referred for a variety of non-specific complaints or as part of a standard workup in known non-cardiac pathologies (e.g. auto-immune disease) but in whom no structural abnormalities of the heart were noted. The presence of TR was not considered pathological if no other structural abnormalities were noted. **"Cardiac hypertrophy"** refers to patients with concentric remodelling, left chamber hypertrophy, isolated septal hypertrophy and hypertrophic cardiomyopathy (with preserved left ventricular systolic function). Patients with myocardial hypertrophy of the basal septum only were not included in this group. When left ventricular systolic function was compromised, patients were classified as "non-ischaemic CMP". **"CAD"** was defined by the presence of atherosclerosis of the coronary arteries with preserved left ventricular systolic function and in the absence of regional myocardial wall contractility abnormalities. **"Ischaemic CMP"** consisted of patients with known coronary artery disease and prior myocardial infarction with a diminished left ventricular systolic function (LVEF ≤ 50%) and/or regional myocardial wall contractility abnormalities. **"Non-ischemic CMP"** refers to patients with a decreased left ventricular systolic function (LVEF ≤ 50%) without evidence of CAD. Patients who had a transient episode of decreased LVEF were still categorized as non-ischaemic cardiomyopathy. **"Valvular heart disease"** was defined as patients with worse than grade 2 mitral regurgitation (MR > 2), worse than or equal to grade 2 aortic valve regurgitation (AR ≥ 2), any sign of elevated transvalvular aortic pressure

gradient or any sign of degenerative or structural valvular lesions. Importantly, patients with isolated right-sided valvular regurgitation were not included in this group. **"Heart transplant"** were patients who underwent heart transplantation. **"Oncologic pathology"** consisted of patients who underwent treatment with chemotherapeutic agents. **"PH"** consisted of patients with type 1, 3, 4 or 5 PH according to the Dana point classification, in use at the time of study design and conduct.[23]

Statistical analysis

First, demographics were explored in the entire population and the predefined groups.

Continuous variables are presented as mean ± SD. Categorical data are presented as frequencies (percentage). Secondly, echocardiographic data of each subgroup were compared with those of patients with a structurally normal heart. To facilitate interpretation, TR severity was dichotomized in non-significant (TR ≤ 2) versus significant TR (TR > 2). For continuous data an unpaired t-test was used, whereas for categorical data a chi square test or a Fisher's exact test was performed. Thirdly, univariate and multivariate (controlling for age, gender, body mass index (BMI) and mean blood pressure) logistic regression was performed to assess the degree of association between significant TR (defined as TR > 2/4) and the different categories of heart disease. Fourthly, correlations (Pearson's correlation coefficient and Spearman's rho where appropriate) were calculated for the severity of TR (0-4/4) and other standard echocardiographic variables. Partial correlations were calculated controlling for known determinants of TR (pulmonary artery pressure, right ventricular dilation, and atrial fibrillation).[24] P < 0.05 was considered significant. All tests were two-tailed. Statistical analyses were performed using SPSS® (version 19, SPSS, Chicago).

Results

Patient selection

A total of 2116 unique consecutive transthoracic echocardiographic studies were retrieved for analysis. Sixty-two patients were excluded: five because they were under 16 years of age, eight because of a right ventricular pacing or shock-lead was present, and 49 because of the presence of complex defects (**figure 1**). Demographic data of the total study population (n=2054) and those of the different subgroups are summarized in table 1. Clinical parameters are listed in table 1 as well. More than 99% of the patients were Caucasian.

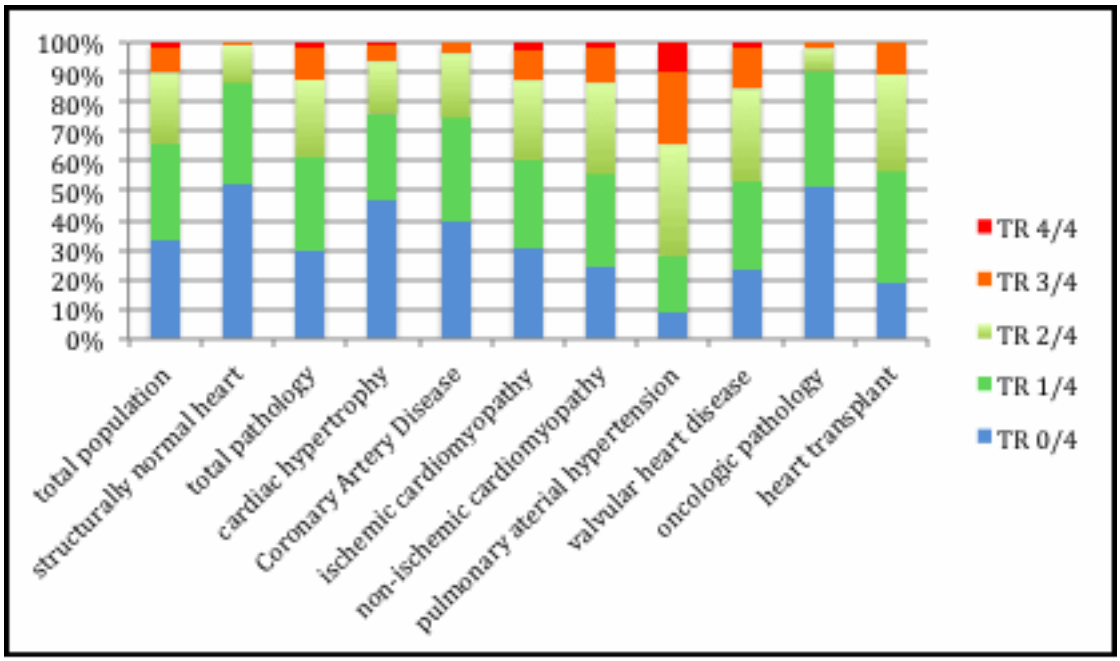
Prevalence of tricuspid valve regurgitation and association with type of heart disease

The prevalence of significant TR was 10.2% in the total population. Significant TR was significantly more prevalent in cardiac hypertrophy (6.5%; P = 0.003), after heart transplantation (10.8%; P < 0.001), ischaemic CMP (12.8%; P < 0.001), non-ischaemic CMP (13.7%; P < 0.001), valvular heart disease (15.7%; P < 0.001), and

PAH (34.4%; P < 0.001) when compared to patients with a structurally normal heart. The distribution of TR across the different subcategories is presented in **figure 2**.

The univariate logistic regression showed an association with significant TR for all groups, except for CAD and oncologic pathology. In multivariate logistic regression, controlling for differences in demographics, significant TR was significantly associated with (in descending order) PAH [OR 35.8 (95% CI 11.7-110.3; P <0.001)], heart transplant [(OR 10.4 (95% CI 3.4-31.8; P < 0.001)], valvular heart disease [OR 6.7 (95% CI 2.3-19.2; P < 0.001)], non-ischaemic CMP [OR 6.2 (95% CI 1.8-21.3; P = 0.004)] and ischaemic CMP (OR 5.6 (95% CI 1.5-21.8; P = 0.012)]. In multivariate logistic regression, significant TR was not significantly associated with CAD, oncologic pathology and cardiac hypertrophy. ORs are summarized in **figure 3**.

Figure 2 Distribution of TR across different subcategories.



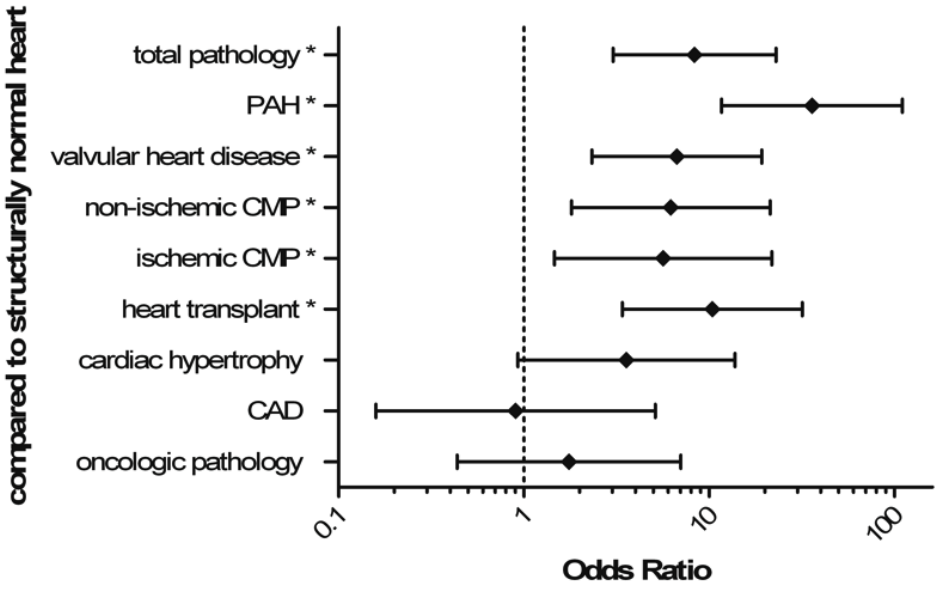
Association of routine echocardiographic variables and TR

Correlations and partial correlations between the degree of severity of TR and all echocardiographic parameters were calculated. In the total population, the highest correlation coefficient was found for PASP (R = 0.512; P < 0.001) followed by the degree of MR (R = 0.455; P < 0.001). When controlling for known determinants of

TR (PASP, RV dilation, atrial fibrillation), TR persisted to correlate with the degree of MR. Correlations are summarized in table 2.

Figure 3 (A) Univariate logistic regression: effect of the dichotomized TR severity (≤ 2/4 vs. > 2/4) on the prevalence of pathology compared to the structurally normal heart. **(B)** Multivariate logistic regression controlled for demographics: age, gender, BMI, mean blood pressure and degree of TR were forced in the model. Categories of pathology were compared with the structurally normal heart. *p < 0.05

A.



B.

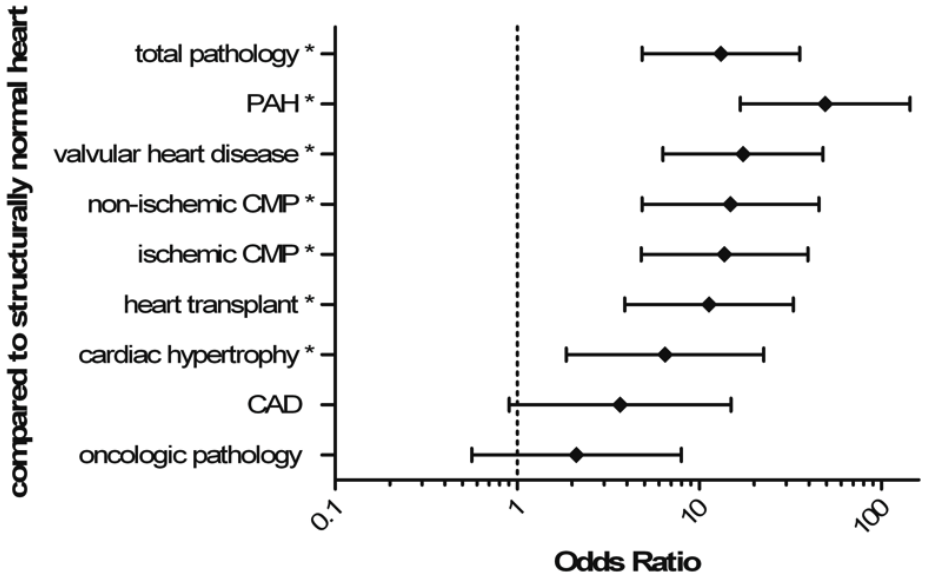


Table 1 Demographic and clinical characteristics of the study population, subdivided in categories of cardiac pathology. Syst BP = systolic blood pressure, diast BP = diastolic blood pressure, mean BP = mean blood pressure, BMI = body mass index, BSA = body surface area, aFib = atrial fibrillation, RV = right ventricle.

	total population	**structurally normal heart**	**cardiac hypertrophy**	**CAD**	**ischemic CMP**	**non-ischemic CMP**	**PAH**	**valvular heart disease**	**oncologic pathology**	**heart transplant**
Total n (%)	2054 (100)	378 (18.40)	108 (5.3)	106 (5.2)	242 (11.8)	117 (5.7)	93 (4.5)	543 (26.4)	226 (11)	241 (11.7)
Age	61.9	49.8	61.7	68.3	71.2	63.3	61.3	69.5	54.3	58.3
Mean (±SD; range)	(± 15.8; 16-98)	(± 16.3; 16-94)	(± 14.7; 22-82)	(± 11.2; 31-88)	(± 10.6; 36-98)	(± 15.2; 21-89)	(± 14.8; 18-86)	(± 12.7; 22-93)	(± 11.5; 18-85)	(± 15; 17-84)
male gender n (%)	1123 (54.7)	179 (47.4)	64 (59.3)	81 (76.4)	200 (82.6)	79 (67.5)	35 (37.6)	261 (48.1)	38 (16.8)	186 (77.2)
mean BP (mmHg)	99.3 (± 14)	99.7 (± 12.8)	102.2 (± 14.6)	98 (± 13.3)	95.5 (± 14.3)	94.1 (± 14.0)	94.2 (± 13.1)	100.9 (± 14.7)	97.9 (± 12,9)	103.6 (± 12.9)
BMI (kg/m2) mean (±SD)	26.3 (± 4.9)	25.5 (± 4.8)	28.3 (± 5.2)	27.6 (± 4.2)	27.2 (± 4.5)	26.8 (± 5.2)	26.7 (± 5.7)	26.5 (± 4.9)	25.6 (± 5)	25 (± 4,4)
Rhythm										
- no aFib n (%)	1898 (92.4)	374 (98.9)	99(91.7)	100 (94.4)	210 (86.8)	91 (77.8)	91 (97.8)	470 (86.6)	225 (99.6)	238 (98.8)
- aFib n (%)	156 (7.6)	4 (1.1)	9 (8.3)	6 (5.7)	32 (13.2)	26 (22.2)	2 (2.2)	73 (13.4)	1 (0.4)	3 (1.2)
RV pacemaker lead n (%)	134 (6.5)	0 (0)	10 (9.3)	3 (2.8)	40 (16.5)	28 (23.9)	1 (1.1)	29 (5.34)	0 (0)	23 (9.5)

Mean BP = mean blood pressure; BMI = body mass index; aFib = atrial fibrillation; RV = right ventricular.

Table 2 Correlations and partial correlations between TR and MR. TR = tricuspid regurgitation, MR = mitral regurgitation, aFib = atrial fibrillation, RV = right ventricular, PASP = pulmonary artery systolic pressure.

		total population	structurally normal heart	cardiac hypertrophy	CAD	ischemic CMP	non-ischemic CMP	PAH	valvular heart disease	oncologic pathology	heart transplant
MR (0-1-2-3-4/4)	**Correlation coefficient**	.455*	.327*	.319*	.608*	.469*	.427*	.400*	.397*	.399*	.413*
		p<0.001	p<0.001	p=0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
	Corrected for PASP, rythm, RV dilation	.392	.273	.272	.557	.343	.343	.426	.335	N/A	.400
		p<0.001	p<0.001	p=0.024	p<0.001	p<0.001	p=0.001	p<0.001	p<0.001	N/A	p<0.001
no aFib/ aFib	**Correlation coefficient**	.220$	.087$	.241$	.197$	.235$	.255$	.195$	.276$	.053$	-.127$
		p<0.001	p=0.092	p=0.012	p=0.043	p<0.001	p=0.006	p=0.06	p<0.001	p=0.429	0.049
	Corrected for PASP, MR, RV dilation	.121	.076	.034	.108	.105	.188	.117	.183	N/A	-.184
		p<0.001	p=0.203	p=0.779	p=0.342	p=0.164	p=0.076	p=0.28	p<0.001	N/A	p=0.008
RV dilation	**Correlation coefficient**	.349$	.026$	.337$	.027$	.327$	.265$	.549$	.327$	-.056$	.143$
		p<0.001	p=0.614	p<0.001	p=0.787	p<0.001	p=0.004	p<0.001	p<0.001	p=0.399	p=0.026
	Corrected for PASP, MR, rythm	.131	-.113	.125	.045	.216	.237	.29	.195	N/A	.19
		p<0.001	p=0.06	p=0.307	p=0.693	p=0.004	p=0.025	p=0.007	p<0.001	N/A	p=0.006
PASP	**Correlation coefficient**	.512*	.374*	.395*	.484*	.555*	.337*	.626*	.484*	,394*	,403*
		p<0.001	p<0.001	p=0,001	p<0.001	p<0.001	p=0,001	p<0.001	p<0.001	p<0.001	p<0.001
	Corrected for RV dilation, MR, rythm	0.369	0.328	0.297	0.429	0.437	0.272	0.499	0.341	N/A	0.379
		p<0.001	p<0.001	p=0.013	p<0.001	p<0.001	p=0.009	p<0.001	p<0.001	N/A	p<0.001

*** Pearson's correlation coefficient; $ Spearman correlation coefficient; MR = mitral regurgitation; aFib = atrial fibrillation; RV = right ventricular; PASP = pulmonary artery systolic pressure.**

Discussion

This study showed that the prevalence of significant TR is 10.2% in the entire study population. It is even more prevalent in PAH, heart transplantation, valvular heart disease, non-ischaemic CMP, and ischaemic CMP. We could confirm that significant TR is associated with the known determinants: elevated pulmonary artery pressure, right ventricular dilatation, and atrial fibrillation. Interestingly, we found a significant correlation between TR and the degree of MR, independently of previously identified determinants.

TR occurs frequently in an echocardiographic protocol, but data are scarce on when and how it should be treated. Although low severity TR is generally well tolerated, significant TR may cause symptoms, biventricular failure and death.[10,12,13] Studies have confirmed that increasing TR severity is associated with worse survival regardless of LVEF or pulmonary artery pressure.[2] Therefore, in recent years, the evaluation of TR has regained interest of the clinician and researcher.

Given the proposed scheme of pathogenesis as described in the introduction, TR should be more abundant in those pathologies that present with high pulmonary artery pressure, RV dilation, primary tricuspid valve disease, as well as atrial fibrillation. Indeed, also in this study, independently of demographic differences between the groups, the finding of TR is significantly more often linked with PAH, valvular heart disease, non-ischaemic and ischaemic CMP and heart transplantation. The first four categories typically present with elevated atrial pressures, higher pulmonary artery pressure, increased pre- and afterload, decreased myocardial function or dilation of the cardiac chambers. The occurrence of TR reflects these underlying haemodynamic changes. However, in transplants, the presence of TR is generally attributed to repetitive RV myocardial biopsies which causes injuries and scarring of both the tricuspid valve and the subvalvular apparatus.[9] Adversely, in patients with CAD, oncologic pathology and cardiac hypertrophy (with preserved left ventricular function), haemodynamic changes are not expected to occur, thus the prevalence of TR was not statistically different from the control group.

Interestingly, after controlling for the known determinants of TR, a significant and independent relation persisted with the degree of MR. This highly significant correlation between TR and MR was even present across all predefined groups,

inclusively the structurally normal heart subgroup. It is possible that apart from the thoroughly described ventricular interdependence, a kind of "valvular interdependence" might exist.[14,25]

Several explanations for this apparent relation are possible, although they remain hypothetical. First, given the close relation of the fibrous tricuspid and mitral annulus, geometric disturbance of the cytoskeleton of the heart may occur if one of the two valves fails. The fibrous skeleton of the heart consists of a stable but deformable platform with two pairs of collagenous prongs spreading from the central fibrous body toward the left and the right, forming the mitral and tricuspid annulus, respectively.[26] The tricuspid annulus in particular is very dynamic and its size and geometry changes with loading conditions.[6,27] In the paediatric population, the interaction between the two annuli of the tricuspid and mitral valve and its importance to maintain normal valve function has been illustrated by 3D echocardiography.[28] In the adult population, the presence of aortic-mitral valve coupling has been evaluated using 3D-transoesophageal echocardiography. The fibrous aortic curtain as part of the cardiac cytoskeleton was indicated as an important contributor to this coupling.[29] These epidemiologic and experimental findings suggest that changes in the mitral valve annulus could thus provoke changes in the geometry of the tricuspid annulus, independently from haemodynamics, and cause TR. Secondly, valvular heart disease could be caused by degeneration of the fibrous skeleton, challenging both the mitral and tricuspid valve. Mitral valve disease may precede tricuspid valve disease, as the mitral valve is subject to higher pressure gradients than the tricuspid valve. This might be the reason why TR continues to evolve although mitral valve disease is stabilized by surgical intervention.[30-32] In this process of simultaneous degeneration, humoral factors may play an important role. The role of matrix metalloproteinase and the renin-angiotensin system in structural remodelling of the volume-loaded heart has been studied both in rats and in a canine model for MR.[33-35] In humans, it has been established that volume overload leads to a loss of interstitial collagen of the myocardium, producing a more compliant ventricle.[36,37] Humoral factors, produced as a consequence of the volume loading caused by a regurgitant valve may alter the entire geometry and structure of the heart as the right and left ventricles share a common biochemical milieu. Thirdly, TR may originate from the haemodynamic changes caused by left-sided heart disease, thus causing functional changes in the

pulmonary circulation and the right ventricle. However, although pulmonary hypertension is a known determinant of TR, elevated PASP does not lead invariably to TR.[38] Vice versa, the resolution of the elevated pulmonary artery pressure after mitral valve surgery does not always eliminate TR and TR often develops years after surgery.[30-32] Fourthly, it is likely that the development of TR is best described by several mechanisms acting simultaneously on the valvular system, with a different contribution of each mechanism in a specific cardiac pathology. As several clinical observations remain unexplained, further research to unveil the contributing factors of TR development is warranted. Further, this may help us to obviate the reluctance to intervene early on the tricuspid valve and to identify patients eligible for correction of tricuspid valve pathology, isolated or in conjunction with mitral valve repair.

Finally, our study has some limitations. Being based on the data from the echo-lab at a tertiary care centre, a selection bias is possible. However, rare pathology was excluded from the analysis. Next, echocardiography is a highly operator-dependent examination. However, due to the large sample size, over- and underestimation of echocardiographic parameters should be evened out. Thirdly, categorizing patients in groups of cardiac pathology remains an artificial process, but it might help to better understand the dataset. Finally, these findings are based on descriptive statistics. A causative relationship between observed factors can thus only be hypothesized.

Conclusions

Our findings show that TR is a common and important finding on routine echocardiography and is present in many different types of heart disease. We could confirm the current concept that significant TR is mainly associated with heart disease that presents with changes in cardiac haemodynamics and related geometry. However, the proposed pathogenesis seems to be incomplete. Independently of known determinants of TR, the degree of MR correlated significantly with TR. We hypothesize a kind of ‘valvular interdependence’. The key to this relation may lie in the cardiac cytoskeleton. More studies are needed to understand the impact of the tricuspid valve on cardiac geometry, haemodynamics, functional capacity, and outcome.

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Chapter 2

Determinants of tricuspid regurgitation and applicability in daily clinical practice.

1. Pulmonary arterial pressure and right ventricular dilatation independently determine tricuspid valve insufficiency severity in pre-capillary pulmonary hypertension.

De Meester P, Van De Bruaene A, Delcroix M, Belmans A, Herijgers P, Voigt J-U, Budts W.

Published in *The Journal of Heart Valve Disease, November 2012*

2. Geometry of the heart and tricuspid regurgitation to exclude elevated pulmonary artery pressure: new insights.

De Meester P, Van De Bruaene A, Herijgers P, Voigt J-U, Delcroix M, Budts W.

Published in *International Journal of Cardiology, October 2013*

1. Pulmonary Arterial Pressure and Right Ventricular Dilatation Independently Determine Tricuspid Valve Insufficiency Severity in Pre- Capillary Pulmonary Hypertension.

Abstract

Background and aim of the study

Elevated pulmonary artery systolic pressure (PASP) causes functional tricuspid valve insufficiency (TI). However, the differential contribution of pressure load and right ventricular (RV) dilatation is not well established. The study aim was to evaluate both variables in relation to TI.

Methods

A cross-sectional study was performed of consecutive transthoracic echocardiographic studies of patients with pre-capillary pulmonary hypertension (PH). Both, demographic data and echocardiographic RV parameters were reviewed. TI was graded semi-quantitatively with colour Doppler Flow imaging. Trend analyses for TI severity (TI grade 0/4, 1/4, 2/4, 3/4, or 4/4) were performed. A proportional odds logistic regression analysis was carried out to identify independent predictors of TI severity.

Results

Eighty-one patients (56 females, 25 males; mean age 60 ± 15 years) with pre-capillary PH were evaluated. Patients with more severe TI had a significantly lower body mass index, a lower mean systemic blood pressure, a shorter pulmonary acceleration time, a higher tricuspid regurgitant gradient, and a more dilated right ventricle. From the echocardiographic parameters, RV dilatation ($p = 0.0143$) and the tricuspid regurgitant gradient ($p = 0.0026$) were independently related to the degree of TI.

Conclusion

In patients with pre-capillary PH, PASP and RV dilatation were both related to the increasing severity of TI. When focusing on TI to improve the prognosis of patients with pre-capillary PH, both PASP and RV dimensions should be taken into consideration.

Introduction

Pre-capillary pulmonary hypertension (PH) is a serious and progressive disease with an important impact on right ventricular (RV) function. Patients with pre-capillary PH have a severely impaired prognosis, and the median survival of patients with pulmonary arterial hypertension (PAH) without treatment is 2.8 years.[1] When therapy is initiated survival is substantially improved, with a one-year survival of 88.4% compared to 71.8% if the patients are left untreated.[1,2] Although specific vasodilator treatment effectively lowers the pulmonary vascular resistance (PVR), the patients will eventually develop RV dysfunction.[3] Most importantly, the patient's characteristics appear to have a substantial impact on their individual prognosis.[4]

Tricuspid valve insufficiency (TI) is a frequent echocardiographic finding, and is most often functional.[5,6] Although functional TI is a frequent occurrence in patients with PAH, and its severity has an impact on functional capacity and prognosis, it is often disregarded in the routine clinical follow up.[7-9] However, significant TI can cause an important additional volume-loading of the right ventricle and, when focusing on TI to reduce the volume overload of the right ventricle, a good understanding of the genesis of TI is necessary.

The determinants of functional TI mostly have been studied in patients with mitral valve disease.[10-13] However, in one retrospective study the determinants of functional TI were identified in patients with an increased pulmonary arterial systolic pressure (PASP), though unfortunately in this case the aetiology of the elevated PASP was not defined.[14] In pre-capillary PH, TI is thought to occur mainly as a consequence of the elevated pulmonary artery pressure (PAP). However, a reduction in PAP after pulmonary endarterectomy (PEA) in patients with chronic thromboembolic pulmonary hypertension does not invariably reduce TI, indicating that other factors are involved.[15]

Hence, the aim of the present study was to examine the determinants of functional TI in patients with precapillary PH.

Clinical material and methods

Patient selection and data acquisition

Patients with pre-capillary PH undergoing transthoracic echocardiography in routine clinical follow-up were retrospectively included from the database of echocardiography between November 2010 and May 2011.

The patients were identified throughout the database of cardiac imaging at the authors' institution, a tertiary care center. The demographic data and echocardiographic parameters were exported to a separate database for statistical analysis. An experienced staff, supervised by a senior cardiologist, performed all echocardiographic studies. The selection process and reviewing of the data were approved by the local ethics committee. No patients were excluded from the analysis.

Echocardiographic parameters

All RV two-dimensional (2D) echocardiographic and Doppler measurements were included for analysis.

The tricuspid regurgitant gradient (TRG) was calculated by the continuous-wave Doppler echocardiographic measurement of peak regurgitant systolic velocity, using the simplified Bernouilli equation ($4*TR\ velocity^2$). The inferior vena cava (IVC) diameter as a surrogate for right atrial pressure was considered as a separate parameter.

Valvular regurgitation severity was graded on a scale of 0 (no regurgitation) to a maximum score of 4, based on semi-quantitative color Doppler flow mapping in all possible incidences with a jet-to-atrial area ratio of <10% termed grade 1, 10-20% grade 2, 20-40% grade 3, and >40% grade 4. The RV diameter was measured at end-diastole at the level of the chordae; dilatation of the right ventricle was defined as none if the diameter was <3.3 cm, mild if between 3.4 and 3.7 cm, moderate if between 3.8 and 4.1 cm, and severe if ≥4.2 cm, or if the RV diameter was larger than the diameter of the left ventricle. Right atrial dimensions were determined at end-systole. The diameter of the IVC was measured at inspiration. Measurements were made according to the criteria of the American Society of Echocardiography.[16]

Statistical analysis

Continuous variables were presented as mean ± SD, or as median and interquartile range (IQR) when appropriate. Categorical data were presented as frequencies and percentages. Initially, all patients were allocated to groups according to the TI severity (0/4, 1/4, 2/4, 3/4, 4/4). Trend analyses for TI severity and demographic and RV parameters were performed using Spearman's rank test and a chi-square analysis when applicable. A univariable proportional odds logistic regression analysis was then performed to determine the degree of association of the studied parameters with the degree of TI severity. Finally, in order to assess independence between the

determinants of TI, a multivariable proportional odds logistic regression was applied to patients in whom values for all studied parameters were present.

A p-value <0.05 was considered to be statistically significant, and all tests were two-tailed. All statistical analyses were performed using SAS for Windows.

Results

The data acquired from 81 echocardiographic studies of unique patients with an established diagnosis of pre-capillary PH were reviewed and analyzed. Diagnosis of PH was made according to current guidelines and patients were classified according to the Dana point classification. (**Figure 1**) Thirty-nine patients (48%) had pulmonary arterial hypertension, 4 (4,9%) had pulmonary hypertension due to lung disease, 37 had chronic thrombo-embolice pulmonary hypertension and in 1 patient (1%), pulmonary hypertension was caused by unclear/multifactorial reasons. Among those patients with pre-capillary PH, 15 had TI 1/4, 29 had TI 2/4, 20 had TI 3/4, and nine had TI 4/4, whereas in eight patients either none or only trace TI was detected. The demographic data (with respective p-values) are listed in Table I. Patients with more severe TI had a significantly lower body mass index (BMI) and a lower mean systemic blood pressure. Patients with a more severe TI presented with a significantly higher TRG, a more dilated right ventricle, a more enlarged IVC, and a shorter pulmonary valve acceleration time (PAT). Echocardiographic 2D and Doppler findings (with respective p-values) are listed in Table II. The distribution of the TRG and of RV dilatation in the different groups of TI severity are shown in **Figures 2 and**

3, respectively.

When performing the multivariable analysis, patients were excluded when values of one or more of the studied parameters were missing (n = 67). From the echocardiographic parameters, RV dilatation (p = 0.0143) and TRG (p = 0.0026) were independently related to the degree of TI. Results from the univariable and multivariable proportional odds logistic regression analysis are listed in Table III.

Figure 1 Type of pre-capillary PH according to the Dana point classification.

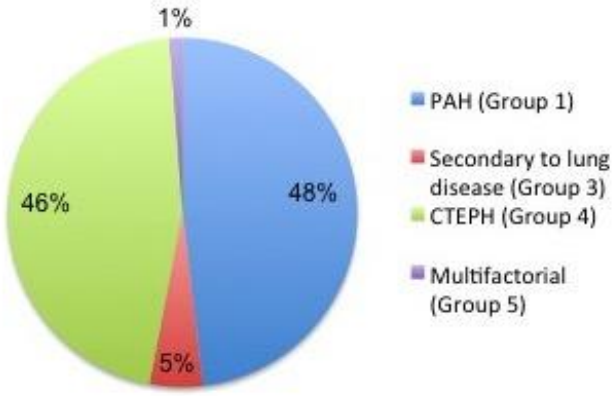

Figure 2 Relationship between TI severity (grade 0 to 4/4) and tricuspid regurgitant gradient (Reg grad). Values are mean ± SD; p-value assessed using Pearson's Rank Correlation test.

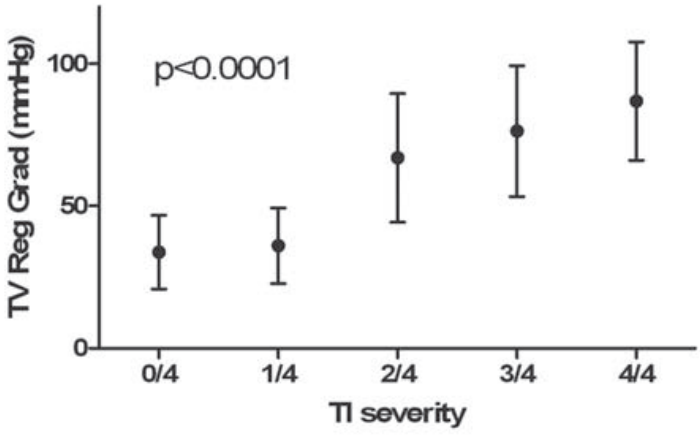

Figure 3 Relationship between TI severity and RV dilatation; p-value assessed using chi-square test for trend.

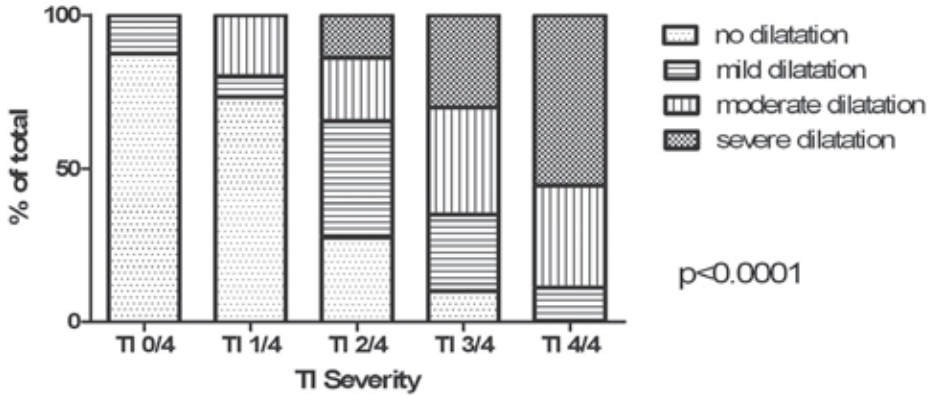

Table 1 Demographics.

	total	**TI 0/4**	**TI 1/4**	**TI 2/4**	**TI 3/4**	**TI 4/4**	**p-value**
Total N	81	8	15	29	20	9	
Age (y) (mean ± SD)	60 (± 15)	61 (± 13)	63 (± 11)	55 (± 17)	62 (± 13)	67 (± 20)	0.4759†
Male gender N(%)	25 (30.9)	5 (62.5)	2 (13.3)	10 (34.5)	4 (20.0)	4 (44.4)	0.6439‡
Mean BP (mmHg) (mean ± SD)	95.1 (± 13.2)	102.8 (± 14.1)	98.8 (± 13.5)	94.9 (± 11.5)	92.5 (± 14.3)	89 (± 12.3)	0.0095*,†
BMI (kg/m^2) (mean ± SD)	26.9 (± 6.0)	29.4 (± 5.4)	29.1 (± 5.4)	26.9 (± 6.1)	26.5 (± 6.3)	22.2 (± 3.5)	0.0024*,†
Rhythm N(%)							
- Sinus	77 (95.1)	8 (100)	14 (93.3)	29 (100)	19 (95)	7 (77.8)	0.188‡
- AFib	3 (3.7)		1 (6.7)		1 (5)	1 (11.1)	
- Pacemaker	1 (1.2)					1 (11.1)	

TI=Tricuspid valve insufficiency; BP=Blood Pressure; BMI=Body Mass Index; AFib=Atrial Fibrillation. *=significant at $p<0.05$; † Spearman's Rank for trend; ‡ Chi square for trend

Table 2 Right Ventricle Echocardiographic parameters.

	total	**TI 0/4**	**TI 1/4**	**TI 2/4**	**TI 3/4**	**TI 4/4**	**p-value**
Total N	81 (100)	8	15	29	20	9	
TV Reg Grad (mmHg) mean (± SD)	63.8 (± 26.9)	33.8 (± 13)	36.1 (± 13.3)	67.6 (± 22.7)	76.4 (± 23.0)	86.9 (± 20.8)	<0.0001*,†
RV dilation n(%)							<0.0001*,‡
- No dilation	28 (34.6)	7 (87.5)	11 (73.3)	8 (27.6)	2 (10.0)	0 (0)	
- Mild dilation	19 (23.5)	1 (12.5)	1 (6.7)	11 (37.9)	5 (25.0)	1 (11.1)	
- Moderate dilation	19 (23.5)	0 (0)	3 (20.0)	6 (20.7)	7 (35.0)	3 (33.3)	
- Severe dilation	15 (18.5)	0 (0)	0 (0)	4 (13.8)	6 (30.0)	5 (55.6)	
PAT (sec) mean (± SD)	83.7 (± 18.7)	95.6 (± 19.9)	95.3 (± 20.6)	79.1 (± 16.1)	80.4 (± 17.9)	73.5 (± 10.4)	0.0026*,†
IVC diameter (mm) median (Q1;Q3)	9.0 (4.0;12.0)	5.0 (0.0;8.0)	7.0 (3.0; 9.0)	9.0 (5.0;11.0)	8.0 (3.5;13.0)	16.0 (13.0;22.0)	0.0022*,†

TI=Tricuspid valve insufficiency; RV=Right Ventricular; TV Reg Grad=Tricuspid Valve Regurgitant Gradient; PAT=Pulmonary Acceleration Time; IVC=Inferior Vena Cava. *=significant at p<0.05; † Spearman's Rank for trend; ‡ Chi square for trend

Table 3 Univariate and multivariate proportional odds logistic regression for TI severity.

		n univariable	Odds Ratio (95% CI) univariable	p- value univariable	Odds Ratio (95% CI) multivariable (n=67)	p-value multivariable (n=67)
TV Reg Grad		78	1.059 (1.038-1.080)	<0.0001	1.040 (1.014-1.066)	0.0026*
RV dilatation	Severe vs. no dilation	81	52.803 (12.505-222.968)	<0.0001	9.043 (1.322-61.855)	0.0143*
	Moderate vs. no dilation		17.187 (4.804-61.486)		8.136 (1.651-40.100)	
	Mild vs. no dilation		9.052 (2.683-30.539)		4.026 (0.928-17.473)	
Gender	Female vs. male	81	1.171 (0.502-2.732)	0.7148	1.463 (0.529-4.043)	0.4631
age		81	1.009 (0.983-1.035)	0.5001	1.013 (0.982-1.045)	0.4131
BMI		81	0.909 (0.848-0.975)	0.0072	0.907 (0.838-0.982)	0.0157*
Mean BP		81	0.959 (0.930-0.990)	0.0089	0.987 (0.948-1.028)	0.5180
PAT		77	0.965 (0.943-0.987)	0.0021	0.991 (0.963-1.021)	0.5627

RV=Right Ventricular; TV Reg Grad=Tricuspid Valve Regurgitant Gradient; PAT=Pulmonary Acceleration Time. [n (%)]; *=significant at p<0.05

Discussion

The study results showed that, in patients with precapillary PH, RV dilatation and elevated PASP, a combination of TVRG and IVC diameter, were both independent and strong determinants of TI severity.

In the past, research focusing on the pathogenesis of TI has been mostly confined to functional TI secondary to mitral valve disease.[13] Studies focusing on isolated TI, which is not caused by left-sided heart disease, have been scarce, although in one study the determinants of moderate and severe TI in patients with elevated PASP due to various reasons were investigated.[14] In this heterogeneous population, RV dilatation, right atrial dilatation, and also PASP all contributed independently to the genesis of TI.[14] Furthermore, the function of the right and left ventricle were interdependent, as dilatation of the right ventricle restricted filling of the left ventricle during late diastole, thus causing a further increase in the PAP.[17,18] Taken together, these findings indicate that not only hemodynamic changes but also changes in the geometry of the right ventricle contribute to the genesis of TI.

In patients with pre-capillary PH, these determinants have not yet been studied. In the present population, it was shown that TI severity was related independently with an increasing RV pressure-load and with increasing RV dilatation. This has been demonstrated in vitro as well as in patients with TI due to left-sided heart disease.[14,15,19-21] The geometric remodeling of the right ventricle most likely originates secondary to the chronic pressure overload of the right ventricle, but may evolve autonomously after structural remodeling has been initiated.

Tricuspid valve insufficiency is a frequent occurrence in the general population and also in patients with PAH.[5] An increasing TI severity has an impact on both prognosis and on functional capacity.[7,8] Although the prognosis of patients with PAH has improved since the introduction of PAH-specific therapies, it is strongly influenced by individual factors.[4] Current therapeutic strategies are focused on lowering the PVR, either pharmacologically or surgically. However, although significant reductions in PVR can be obtained, its normalization is seldom achieved and consequently, over a period of time, progressive RV failure will occur and the patient's functional status will further decline.[3] This indicates that, in order to improve prognosis, attention

should be focused more on the entire hemodynamic status of the patient, rather than on the PVR and PAP alone.

With this goal in mind, and as TI is a known cause of volume overload of the right ventricle, TI should be taken into account when performing diagnostic testing in patients with PAH. Furthermore, the results of the present study confirm that geometric remodeling plays an important role in maintenance of the TI induced volume-overload of the right ventricle. Consequently, the follow up examination should also focus on geometric remodeling of the right ventricle.

Indeed, a supplemental and prolonged volume-overload in a pressure-loaded right ventricle leads to RV failure.[22] Attempts to lower the PVR and PAP might be less effective when dilatation of the right ventricle is present, as right-sided volume-overload might persist. Hence, the presence of TI might warrant a more aggressive therapy to improve the prognosis of patients with PAH.

Study limitations

The primary limitation was that the study findings were based on descriptive statistics in an ad hoc analysis of patients at routine follow up. Second, echocardiography is an operator-dependent examination. Third, right atrial enlargement was not taken into account because no effective data on right atrial dimensions were available. However, as the RV and right atrial dimensions were closely correlated, it was considered that the introduction of right atrial dimensions into the model would not have altered the findings.

Conclusion:

In conclusion, in patients with PAH, hemodynamic changes due to the elevation of PASP, as well as geometric changes of the right ventricle, are independently related to TI severity. Hence, a more aggressive therapy in patients with PAH might be warranted if significant TI were to be noted at echocardiographic follow up examination.

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2. Geometry of the heart and tricuspid regurgitation to exclude elevated pulmonary artery pressure: new insights.

Abstract

Objectives

The value of the right heart morphology is not well established for the evaluation of elevated pulmonary artery pressure (PAP). We aimed (1) to assess the relationship between right heart morphology and PAP and (2) to evaluate whether morphology can help to exclude elevated PAP.

Methods

From 11-2010 until 01-2011, 1640 consecutive patients were included from the database of echocardiography. Tricuspid regurgitation (TR) severity, right ventricular (RV) dilatation and right atrial (RA) dilatation were evaluated for (1) tricuspid regurgitant gradient (TRG) ≤ 30 mm Hg; (2) TRG = 30–40 mm Hg, and (3) TRG > 40 mm Hg. A weighted score model was developed to diagnose TRG > 30 mm Hg. The model was validated with data from right heart catheterization in 100 patients.

Results

TR severity and RA diameter increased significantly from group 1 to group 2 and to group 3 whereas RV diameter differed only significantly from group 2 to group 3. To integrate TR severity, RA dilatation and RV dilatation, a point-based model was constructed. A total score ≥ 3 was associated with a sensitivity and specificity of 95% and 31% and with a positive and negative likelihood ratios of 1.37 and 0.17, respectively to diagnose TRG > 30 mm Hg. Negative predictive value for TRG > 30 mmHg was 92%. Prediction numbers could be reproduced when right heart catheterization was used as a reference standard.

Conclusions

Increasing TRG is characterized by a steady increase in TR severity and RA dilatation. However, the RV dilates only significantly when TRG is markedly elevated. Integrating morphological parameters could reliably exclude the presence of elevated TRG and thus can be useful in screening for elevated PAP.

Introduction

Elevated pulmonary artery pressures (PAP) can be present in a variety of diseases and can severely impair prognosis, however, the diagnosis remains difficult.[1, 2] An exact measurement of PAP can only be obtained by right heart catheterization (RHC).[3, 4] However, RHC is an invasive procedure that is associated with a risk for serious adverse events and mortality.[5] Therefore, non-invasive imaging modalities are used to provide estimates of PAP.[6] Currently, the best echocardiographic estimate of systolic PAP is calculated by adding an estimated right atrial pressure (RAP) to the tricuspid regurgitant gradient (TRG) obtained by continuous wave (CW) Doppler echocardiography.[7, 8] However, the measurement can only be acquired in 75-90% of patients in experienced hands and even then suboptimal CW traces are often obtained.[8, 9]

If a good CW Doppler signal cannot be obtained, other measurements are proposed, including amongst others right ventricle ejection time, isovolumic relaxation time or right ventricular anterior wall thickness, and pulmonary acceleration time but none have been implemented in routine clinical practice often because of difficulties obtaining reproducible measurements.[10-16] Pulmonary hypertension guidelines indicate that changes in right heart morphology should be taken into account when evaluating a patient suspect for elevated PAP.[3] Unfortunately, the value of these measurements is not established yet and instructions on what should be measured are not given. Therefore, we aimed (1) to assess the relationship between right heart morphology and elevated PAP and (2) to evaluate if morphology can help to exclude patients with elevated PAP.

Methods

Population and echocardiographic analysis

The digitalized echocardiographic database at the University Hospitals of Leuven was searched for all adult patients in whom a transthoracic echocardiographic study was done between November 2010 and January 2011. A total of 2054 unique patients were retrieved from the database. Patients with intracardiac shunts were excluded. TRG was calculated by means of the simplified Bernouilli equation (4 times velocity

squared). Only those patients in whom tricuspid regurgitant velocities could be obtained were included for analysis (n=1640). Based on TRG, patients were divided into 3 groups: (1) TRG ≤ 30 mmHg; (2) TRG = 30-40 mmHg and (3) TRG > 40 mmHg.[3, 17]

Indications for echocardiography included: "arterial hypertension", known or suspect "ischemic heart disease", known or suspect "valvular heart disease", known or suspect "cardiomyopathy", known or suspect "non-cardiac pulmonary hypertension", "oncology" treated with cardiotoxic drugs and work-up pre- or post-"transplant" (kidney, lung, liver and heart). Lastly a group "miscellaneous" included patient referred for a variety of reasons being, pre-operatively, because of palpitations, syncope, neuro-muscular disorders, atypical chest pain, suspect for endocarditis and systemic disease screening.

Right heart parameters studied included the severity of tricuspid regurgitation (TR), right ventricular (RV) and right atrial (RA) dilatation. TR severity was graded semi-quantitatively based on colour Doppler echocardiography. The RV diameter was measured at end-diastole at the mid-ventricular level and was considered normal if RV diameter was smaller than 33 mm, mild dilatation if diameter was between 34 and 37 mm, moderate dilatation if diameter was between 38 and 41 mm and severe dilation if diameter was larger than or equal to 42 mm.[18] Categories were considered as ordinal variables and were numbered 0 (no dilatation) to 3 (severe dilatation). The RA long-axis dimensions were measured at end-systole and was considered normal if RA measured smaller than 53 mm, mild dilation if long-axis diameter was between 53-57 mm, moderate between 58 to 60 mm and severe dilation >60mm.[19] Categories were again considered as ordinal variables and were numbered accordingly 0 to 3. Acceleration time of pulmonary artery systolic flow (PAT) was measured from the PW Doppler tracings at the right ventricular outflow tract.[18, 19]

Statistical analysis

Continuous variables are presented by means and standard deviations. Categorical variables are presented using observed frequencies and percentages.

First, comparative statistics were calculated with an analysis of variance (one-way ANOVA). Post-hoc test with Bonferroni-adjusted p-values were calculated subsequently. Second, multivariable logistic regression for TRG > 30 mmHg was

performed to obtain the regression coefficients for RA dilatation, RV dilatation and TR severity. Regression coefficients were determined by bootstrapping with resampling from 1,000 simulations thus obtaining a representable value for each parameter and improving prediction accuracy in the total population. Based on the regression coefficients, points were determined for each category of the right heart parameters to construct a weighted score model for diagnosing TRG > 30 mmHg. Next, probabilities associated with point totals were calculated.[20]

Third, the score model was compared with PAT to predict TRG > 30 mmHg by means of a ROC analysis on the study sample. Sensitivity, specificity, positive likelihood ratio (LHR+), negative likelihood ratio (LHR-) were calculated appropriately. For the studied sample, positive predictive value (PPV) and negative predictive value (NPV) were calculated as well. Based on the calculated likelihood ratio, the post-test probability for a negative and a positive test was plotted for increasing prevalence of elevated pulmonary artery pressure in the studied population.

Finally, a subset of patients that underwent right heart catheterisation was used as a validation cohort for the score model. Patients with an invasively measured mean PAP $\geq$ 25 mmHg were diagnosed with pulmonary hypertension.[3] Corresponding echocardiographic data of transthoracic echocardiography were used to calculate the corresponding score and to assess the post-test probability of having elevated pulmonary artery pressure. For these patients in whom right heart catheterisation was performed, the predicted post-test probability to exclude pulmonary hypertension was compared with the definite diagnosis of pulmonary hypertension as obtained from invasive measurements of the mean PAP.

Data were analyzed using SPSS® (version 20, SPSS, Chicago). The local ethics committee approved the selection process and the review of the data.

Table 1 Demographic and clinical characteristics of the study population

	Total	TRG obtainable				TRG not obtainable
		Total	**Group 1 TRG ≤ 30 mmHg**	**Group 2 TRG 30-40 mmHg**	**Group 3 TRG > 40 mmHg**	
n (%)	2014 (100%)	1640 (79.8%)	1146 (69.9%)	289 (17.6%)	205 (12.5%)	414 (20.2%)
Demographics						
Male gender, n (%)	1123 (54.7%)	871 (53.1%)	614 (53.6%)	161 (55.7%)	96 (46.8%)	252(60.9%)
Age, y (mean±SD)	62±16	63±16	59±16	70±12	71±14	59±15
Atrial Fibrillation, n (%)	156 (7.6)	136 (8.3%)	54 (4.7%)	47 (16.3%)	35 (17.1%)	20 (4.8%)
Mean BP, mmHg (mean±SD)	99±14	99±14	99±13	102±15.4	96±14	100±15
Weight, kg (mean±SD)	75 ± 15	74±16	74±15	75±16	72±16	77±15
BMI, kg/m^2 (mean±SD)	26,3 ± 4.9	26.1±4.9	25.8±4.5	27.2±5.4	26.5±5.6	26.9±4.9
Echocardiography						
TR severity x/4 (mean±SD)	1.12±1.020	0.98 ± 0.024	1.05 ± 0.85	1.80 ± 0.87	2.35 ± 0.89	0.23±0.61
RA dilatation x (mean±SD)	0.51±0.84	0.57 ± 0.88	0.35 ± 0.67	0.88 ± 0.98	1.40 ± 1.11	0.28 ±0.60
RV dilatation x (mean±SD)	0.12±0.47	0.14 ± 0.50	0.05 ± 0.28	0.10 ± 0.40	0.71 ± 0.99	0.04± 0.28
Indication						
Arterial hypertension	55 (2.7%)	39 (2.4%)	29 (2.5%)	7 (2.4%)	3 (1.5%)	16 (3.9%)
Ischemic heart disease	352 (17.1%)	265 (16.2%)	173 (15.1%)	58 (20.1%)	34 (16.6%)	87 (21.0%)
Valvular heart disease	536 (26.1%)	461 (28.1%)	273 (23.8%)	118 (40.8%)	70 (34.1%)	75 (18.1%)
Cardiomyopathy	142 (6.9%)	113 (6.9%)	74 (6.5%)	25 (8.7%)	14 (6.8%)	29 (7.0%)
Non-cardiac PH	90 (4.4%)	88 (5.4%)	8 (0.7)	13 (4.5%)	67 (32.7%)	2 (0.5%)
Oncology	257 (12.5%)	185 (11.3%)	165 (14.4%)	15 (5.2%)	5 (2.4%)	72 (17.4%)
Transplant	297 (14.5%)	251(15.3%)	206 (18.0%)	37 (12.8%)	8 (3.9%)	46 (11.1%)
Miscellaneous	325 (15.8%)	238 (14.5%)	218 (19.0%)	16 (5.5%)	4 (2.0%)	87 (21.0%)

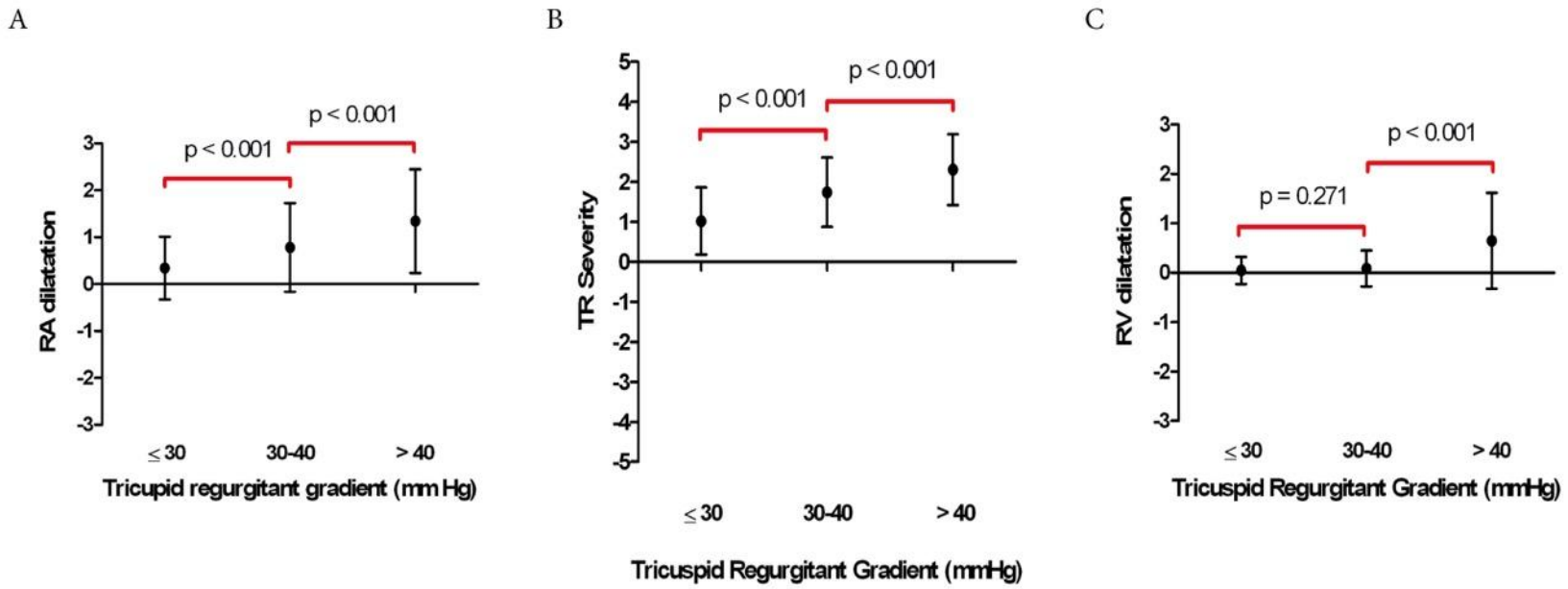
TRG: tricuspid regurgitant gradient; BP: blood pressure; BMI: body mass index; PH: pulmonary hypertension

Table 2 Differences in right heart parameters between groups

	Total	**Group 1** **TRG ≤ 30 mmHg**	**Group 2** **TRG 30-40 mmHg**	**Group 3** **TRG > 40 mmHg**	**p-value** **ANOVA**	**p-value** **1 vs. 2**	**p-value** **2 vs. 3**
n (%)	1640 (100%)	1146 (69.9%)	289 (17.6%)	205 (12.5%)			
TR severity x/4 (mean±SD)	0.98 ± 0.024	1.05 ± 0.85	1.80 ± 0.87	2.35 ± 0.89	<0.001	<0.001	<0.001
RA dilatation x (mean±SD)	0.57 ± 0.88	0.35 ± 0.67	0.88 ± 0.98	1.40 ± 1.11	<0.001	<0.001	<0.001
RV dilatation x (mean±SD)	0.14 ± 0.50	0.05 ± 0.28	0.10 ± 0.40	0.71 ± 0.99	<0.001	0.271	<0.001
PAT, ms (mean±SD)	110±29	116±27	101±26	90±26	<0.001	<0.001	<0.001

TRG: tricuspid regurgitant gradient; TR: tricuspid regurgitation; RA: right atrium; RV: right ventricle; PAT: pulmonary acceleration time; RA dilation graded 0 (no dilatation) to 3 (severe dilatation); RV dilatation graded 0 (no dilatation) to 3 (severe dilatation).

Figure 1 Comparison of **(A)** RA dilatation between groups, **(B)** TR severity between groups and **(C)** RV dilatation between groups; mean ± SD.



Results

Population and morphological changes

A total of 2054 patients were retrieved from the database. Tricuspid regurgitant velocities could be obtained in 78.8% of patients (n=1640). Demographics and echocardiographic parameters are listed in **Table 1 and 2**.

The indication to perform echocardiography and the prevalence of the echo alterations in each subgroup is described in **Table 1 and 3**.

TR severity and RA dilation increased significantly from group 1 to group 2 and to group 3 (One-way ANOVA with Bonferroni post-hoc $p<0.001$) **(Fig. 1A and 1B)**. RV dilatation differed only significantly from group 2 to group 3 (one-way ANOVA with Bonferroni post-hoc test $p=0.271$ and $p<0.001$ respectively) **(Fig 1C).**

Table 3 Differences in right heart parameters for each indication for echocardiography.

	TR severity	**RA dilatation**	**RV dilatation**
	x/4 (mean ± SD)	x (mean ± SD)	x (mean ± SD)
Arterial hypertension	0.76 ± 0.860	0.45 ± 0.662	0.02 ± 0.135
Ischemic heart disease	1.13 ± 1.025	0.72 ± 0.866	0.09 ± 0.371
Valvular heart disease	1.42 ± 1.045	0.75 ± 0.934	0.09 ± 0.381
Cardiomyopathy	1.37 ± 1.082	0.97 ± 1.098	0.19 ± 0.595
Non-cardiac PH	2,1 ± 1,086	1,32 ± 1,084	1,22 ± 1,124
Oncologic	0.61 ± 0.721	0.14 ± 0.443	0.01 ± 0.108
Transplant	1.24 ± 0.944	0.05 ± 0.242	0.07 ± 0.316
Miscellaneous	0.61 ± 0.724	0.21 ± 0.509	0.02 ± 0.135

PH: pulmonary hypertension; TR: tricuspid regurgitation; RA: right atrium; RV: right ventricle; RA dilation graded 0 (no dilatation) to 3 (severe dilatation); RV dilatation graded 0 (no dilatation) to 3 (severe dilatation).

Score model to exclude elevated TRG

Multivariate regression analysis showed that TR severity, RA and RV dilatation were independently related to TRG > 30 mmHg **(Table 4).** A scoring model was constructed based on TR severity, RA and RV dilatation. The score of each parameter is listed in **Table 4**. ROC-analysis to differentiate between TRG ≤ 30 mmHg and TRG > 30 mmHg was performed for the scoring model (AUC=0.808; CI 0.781-0.834; p<0.0001) and for PAT (AUC=0.716; CI 0.685-0.748; p<0.0001) **(Fig 2).** Sensitivity, specificity, LHR+ and LHR- are listed in **Table 5.** Post-test probability for a positive and a negative test is plotted for different prevalence **(Fig 3).** The prevalence of patients with a TRG ≥ 30 mmHg was 36%. A score ≥ 3 corresponded with a positive predictive value of 43% and a *negative predictive value of 92 %*. When compared to PAT < 100 msec, positive and negative predictive value was 56% and *77%*, respectively and for PAT < 120 msec was this 45% and *83%*, respectively.

Table 4 Logistic regression to predict TRG > 30 mmHg

	log regression bèta	**log regression p-value**		**points**
RA	0,457	<0,0001	no dilatation	0
			mild dilatation	1
			moderate dilatation	2
			severe dilatation	3
RV	0,377	0,016	no dilatation	0
			mild dilatation	1
			moderate dilatation	2
			severe dilatation	2
TR severity	1,071	<0,0001	0/4	0
			1/4	2
			2/4	4
			3/4	6
			4/4	8

RA: right atrium; RV: right ventricle; TR: tricuspid regurgitation

Figure 2 Receiver operator characteristics curve for PAT and Score. PAT = pulmonary artery systolic flow acceleration time.

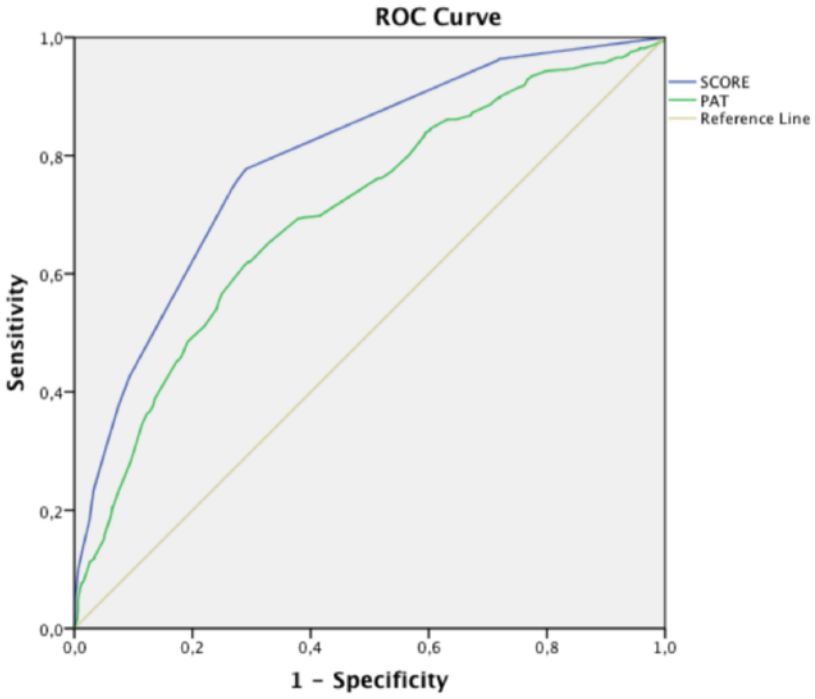
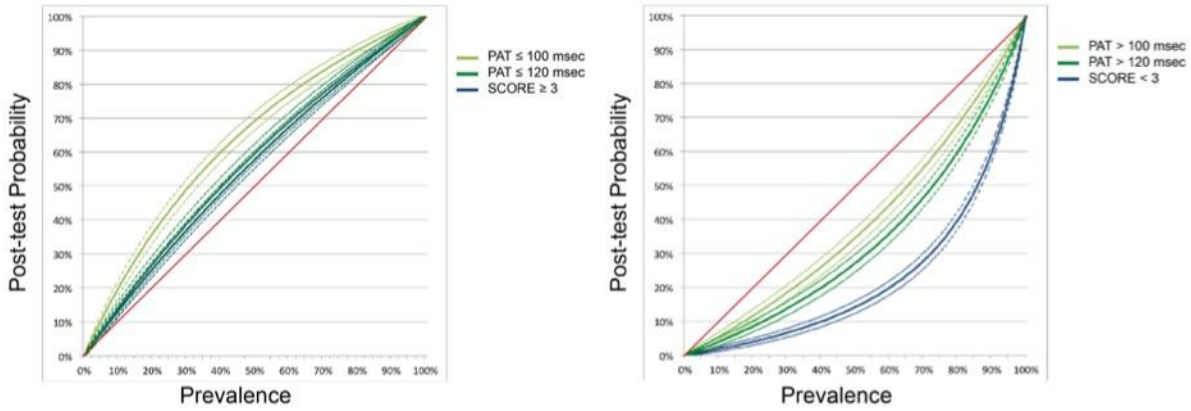


Table 5 Performance of diagnostic test to predict TRG > 30 mmHg

	SCORE ≥ 3	**PAT < 100 ms**	**PAT < 120 ms**
	"= TRG>30 mmHg"	"= TRG>30 mmHg"	"= TRG>30 mmHg"
Sensitivity; % (95% CI)	94.9% (93.7-96.0)	61.5% (58.7-64.4)	83.9% (81.8-86.1)
Specificity; % (95% CI)	30.8% (28.4-33.2)	72.5% (70.0-75.2)	43.1% (40.2-46.0)
Positive Likelihood Ratio	1.37	2.25	1.47
Negative Likelihood Ratio	0.17	0.53	0.37
Prevalence	36%	36%	
Positive predictive value; % (95% CI)	43.2% (40.7-45.8)	55.6% (52.6-58.5)	45.1% (42.2-48.0)
Negative predictive value; % (95% CI)	91.5% (90.1-93.0)	77.2% (74.8-79.7)	82.8% (80.6-85.0)

PAT: pulmonary acceleration time; TRG: tricuspid regurgitation gradient

Figure 3 Post-test probability relative to the presence of the studied population for a **(A)** positive test and **(B)** negative test. PAT = pulmonary artery systolic flow acceleration time.



Evaluation of the model using right heart catheterisation

The prevalence of mean pulmonary artery pressure ≥ 25 mmHg in this subset of patients was 75%. Based on the LHR-, our model predicts that a score < 3 should lower the post-test probability for pulmonary hypertension from 75% to 33% **(Fig. 3)** and corresponds to an *expected negative predictive value of 67%*. The results from the right heart catheterisation compared with the score-model are summarized in **Table 6.** Score < 3 decreased the pre-test probability from 75% to 26% as compared to 33% predicted by the model, corresponding with a *measured negative predictive value of 74%*.

Table 6 Comparison of the score-model with the invasively determined diagnosis of pulmonary hypertension. Expected predictive values, determined based on the likelihood ratios are compared with the calculated values from the validation cohort. (n=number)

	MeanPAP < 25 mmHg	MeanPAP ≥ 25 mmHg	total
Score < 3 (n)	17	6	**23**
Score ≥ 3 (n)	8	69	**77**
	25	**75**	**100**
	Expected predictive values based on the LHR+ and LHR-	**Measured predictive values from right heart catheterisation**	
Prevalence	75%	75%	
Positive predictive value; % (95% CI)	80% (78-83)	90 % (84-96)	
Negative predictive value; % (95% CI)	67% (64-69)	74 % (65-83)	

Discussion

First, this study shows that increasing TRG is characterized by a steadily increase in TR severity and RA dilatation. However, the RV dilates only significantly when TRG is markedly elevated. Secondly, the score-model based on right heart geometry and TR severity gives a good indication of the absence of pulmonary hypertension. When patients are screened for different clinical reasons by echocardiography, elevated PAP always needs to be excluded. RHC remains the gold standard to diagnose PH, but cannot be used as a screening tool. Therefore, PAP is estimated by TRG based on CW Doppler findings. When TRG cannot be obtained by echocardiography, alternatives to screen for elevated PAP are scarce. In daily practice the most utilised alternative to exclude the presence of elevated PAP is the measurement of PAT as determined by PW Doppler tracings at the right ventricular outflow tract.[10, 11] However, this measurement is variable and dependent on heart rate.[11]

PH is known to induce changes at the level of the right heart. Therefore, we wanted to investigate if the use of simple morphological criteria could exclude elevated PAP. It

is common practice that when the morphology of the right heart appears normal, elevated PAP is considered excluded, although this is not formally confirmed in the literature. Moreover, many physicians conclude that elevated PAP is excluded when the RV diameter is normal, but again, there are no data to support this. Therefore, we decided to select a large study sample of examinations from our department of echocardiography within a specific time period. This sample would provide us with enough morphologic information on the right heart, throughout different diseases. Because it was not possible to perform a RHC in all these patients, we compared the morphologic data with the TRG as a surrogate for PAP. For this purpose, the patient population was divided in 3 TRG categories. It is an on-going discussion which cut-off values for TRG should be used in the screening for elevated PAP, therefore the cut-offs of TRG in our study were arbitrary but were based on a literature search and are currently used in our centre.[3, 17, 21, 22] In patients with a TRG ≤ 30 mmHg, the diagnosis of PH is very unlikely. If the calculated TRG is between 30 and 40 mmHg and even more so if TRG is > 40 mmHg, a significant number of patients can be diagnosed with PH by RHC.[21, 22]

In our study, the RV diameter was not significantly enlarged in those patients with a TRG between 30 and 40 mmHg when compared to those with a TRG ≤ 30 mmHg. As discussed earlier, in clinical practice, when RV dimensions are normal, the presence of elevated PAP is often ruled out. Based on these data, we have to conclude that the RV seems to dilate only in a later stage (if TRG > 40 mmHg) and, therefore, normal RV dimensions do not preclude the presence of increased PAP. RA dilatation and TR severity, however, show a steadily increase along the 3 categories. On the other hand, referring to table 3 and **Figure 1 and 3**, RA and RV dimensions might still be normal in the presence of clearly elevated PAP (group 3).

Analysing these data, we decided that an integrative approach, combining several right heart parameters would yield a powerful, reliable and easy method to exclude the presence of elevated TRG. We decided not to evaluate the diameter of the inferior vena cava, as dilatation can occur in a range of pathologies as well as in sporty young adults without elevated PAP. Also, we did not focus on RV wall thickness as this is hard to measure in a standardized way and only significantly increases in patients with severe PH. Multivariate logistic regression showed in all 3 variables a strong and

significant relationship with TRG > 30 mmHg and a score-model was build. **Figure 2** and 3 show the performance of the score-model as well as a comparison with the currently applied cut-off values for PAT. A score < 3 reliably ruled out the presence of elevated pulmonary pressures as indicated by the negative LHR of 0.17. On the other hand, a positive test (i.e. a score ≥ 3) did not contribute importantly to the diagnosis of pulmonary hypertension (positive LHR = 1.37). Importantly, the predictive value of a test is highly influenced by the prevalence of the disease in the studied population. This is illustrated in **Figure 3**. This indicates that, based on this cut-off value, the presence of elevated PAP can be reliably excluded in low-risk populations if the test is negative. A positive test, however, did not add much information to the evaluation. Compared to PAT, the score-model excluded more reliably the presence of elevated PAP. Furthermore, in this sample, PAT was not helpful to diagnose elevated PAP as well, with a positive LHR comparable to a score ≥ 3.

Because controversy exists whether TRG is an accurate measurement of PAP, we validated the model in a subset of patients in whom invasive measurements were obtained and thus having a certain diagnosis of pulmonary hypertension.[22] In this subset of patients, the prevalence of pulmonary hypertension was high and hence, negative predictive values would be unsatisfactory in clinical practice. It is obvious that this patient population would not qualify for a screening test, as the pre-test probability is very high. However, for the purpose of the study, we used this population to determine if our model reliably predicted the post-test probability of a positive and a negative test. We obtained similar results indicating that our model can be applied to exclude the presence of pulmonary hypertension.

Combining several right heart parameters thus helps to exclude the presence of elevated PAP, as is indicated but not elaborated in the current guidelines on pulmonary hypertension.[3]

Limitations

Several limitations should be noted. First, although this study sample was large and spread in time, there might be always a selection bias. Second, the accuracy of the model could probably be improved when including more variables; however, this

adds to the complexity of the model and we believe that RA and RV dimensions, and TR severity are the easiest to obtain with high reproducibility.

Conclusion

This study showed that increasing TRG is characterized by a steadily increase in TR severity and RA dilatation. However, RV dilates only significantly when TRG is markedly elevated. An integrative approach to the patient with suspected elevated PAP is necessary, even more so if no good CW traces of the tricuspid valve can be obtained. The score-model based on geometry and TR severity could reliably exclude the presence of pulmonary hypertension in a low-risk population.

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Chapter 3

Exercise in the pressure-loaded ventricle and its impact on tricuspid regurgitation severity.

1. Increased pulmonary artery pressures during exercise are related to persistent tricuspid regurgitation after ASD2 closure

De Meester P, Van De Bruaene A, Herijgers P, Voigt J-U, Vanhees L, Budts W.

Published in *Acta Cardiologica, August 2013*

2. Functional and hemodynamic assessment of mild to moderate pulmonary valve stenosis at rest and during exercise.

De Meester P, Buys R, Van De Bruaene A, Gabriels C, Voigt J-U, Vanhees L, Herijgers P, Troost E, Budts W.

Published in *Heart, September 2014*

3. Pilot trial: The impact of right ventricular contractile reserve on tricuspid regurgitation severity in patients with repaired tetralogy of Fallot.

1.Increased pulmonary artery pressures during exercise are related to persistent tricuspid regurgitation after atrial septal defect closure

Abstract

Objective

Although closure of an atrial septal defect type secundum often normalizes right heart dimensions and pressures, mild tricuspid insufficiency might persist. This study aimed at (1) identification of determinants, which could explain the persistence of tricuspid insufficiency after atrial septal defect closure and (2) evaluation of functional capacity of patients with persistent mild tricuspid insufficiency.

Methods and results

Twenty-five consecutive patients (age 42±17y) were included from the outpatient clinic of congenital heart disease at the University Hospitals of Leuven. All underwent transthoracic echocardiography, semi-supine bicycle stress echocardiography and cardio-pulmonary exercise testing. Six (24%) had mild tricuspid insufficiency (2/4) compared to 19 (76%) with no or minimal tricuspid insufficiency (≤1/4) as assessed by semi-quantitative colour Doppler echocardiography. Mann-Whitney U and Fishers Exact tests were performed where applicable. Patients with persistent mild tricuspid insufficiency were significantly *older* than those with no or minimal tricuspid insufficiency (p=0.042). At rest, no differences in right heart configuration, mean pulmonary artery pressure or right ventricular function were found. At peak exercise, *mean pulmonary artery pressure* was significantly higher in patients with mild persistent tricuspid insufficiency (p=0.026). Peak oxygen uptake was significantly lower in patients with mild persistent tricuspid insufficiency (p=0.019).

Conclusions

Mild tricuspid insufficiency after atrial septal defect repair occurs more frequently in *older* patients and in patients with higher *mean pulmonary artery pressure* at peak exercise. In patients with mild tricuspid insufficiency, functional capacity was more

reduced. Mild tricuspid insufficiency could be a marker of subclinical persistent pressure load on the right ventricle.

Introduction

Atrial septal defect type secundum is a common congenital heart defect with a prevalence of 1.43 in 1000 live births.[1] Patients with an atrial septal defect present with a volume-overload of the right heart which leads to right ventricular and right atrial dilatation, decreased right ventricular function and finally right heart failure.[2, 3] Furthermore, pulmonary arterial pressure is frequently elevated.[4, 5]

Tricuspid insufficiency is a common finding in patients with an atrial septal defect and is caused by a combination of elevated pulmonary artery pressure, right ventricular and tricuspid annulus dilatation, and an impaired right ventricular function.[6] Moreover, increasing tricuspid insufficiency severity is associated with worse prognosis and decreased functional capacity.[7, 8] Also after atrial septal defect closure, a persistent significant tricuspid insufficiency seems to be related with increased cardiovascular morbidity and mortality.[6]

The reason why tricuspid insufficiency often persists after atrial septal defect closure, although pulmonary artery pressures at rest as well as right heart configuration normalizes, remains unknown.[9-14] However, a recent study has shown that in patients with late atrial septal defect closure, although pulmonary artery pressure was normal at rest, pulmonary artery pressure increases more during exercise compared to patients who had an early intervention.[15] We hypothesized that this abnormal increase in pulmonary artery pressure during exercise could maintain subtle morphological changes of the right heart and thus keeps tricuspid insufficiency.

This study aimed at (1) the identification of determinants, which could explain the persistence of tricuspid insufficiency after atrial septal defect closure (including pulmonary artery pressure during exercise) and (2) the evaluation of functional capacity of patients with persistent mild tricuspid insufficiency after atrial septal defect closure.

Materials and Methods

Patient selection and data collection

Patients were retrieved from the outpatient clinic of congenital heart disease at the University Hospitals of Leuven between the 10^{h} of March and the 17th of November 2009. Patients had to have an atrial septal defect closed in the past and had to be older than 17 years. Further, patients with known coronary artery disease, significant valvular disease other than mild tricuspid or mitral regurgitation (>2/4), pulmonary disease, pulmonary embolism, concomitant congenital heart disease, a history of arrhythmias or current arrhythmias were excluded from the study. At the moment of inclusion, informed consent was obtained from all participants. The local ethics committee approved the data collection.

Demographics

Gender, age, and clinical characteristics were retrieved from the patients' records. Mean blood pressure was calculated from the diastolic and systolic blood pressure values [(2 * diastolic blood pressure + systolic blood pressure) / 3].

Transthoracic echocardiography en bicycle stress echocardiography

All patients underwent a standard transthoracic echocardiographic examination. All examinations were performed on a Vivid 7 or 9 ultrasound system (General Electric Vingmed Ultrasound, Horten, Norway) equipped with a 3 Mhz probe. Exercise echocardiography was performed on a semi-supine ergometer tilted laterally from 20° to 30° to the left (Easystress, Ecogito Medical sprl. Liège, Belgium). The protocol started at 25 watts with an increment of 25 watts every 2 minutes until the maximum tolerated load. Blood pressure and 12-lead ECG were recorded at rest and every 2 minutes during exercise.

A single observer performed the measurements. All measurements were made in triplicate. Analysis was done off-line using dedicated software (EchoPac BT08, General Electric Vingmed Ultrasound, Horten, Norway).

In all patients, a complete resting echocardiographic study was performed in the supine position. All Doppler echocardiographic and Doppler tissue imaging recordings were obtained during normal respiration. At rest, valvular insufficiency of the atrioventricular valves was evaluated semi-quantitatively by colour Doppler flow

mapping with a jet-to-atrial-area ratio of <10% termed grade 1, 10-20% grade 2, 20-40% grade 3 and > 40 % as grade 4. Care was taken in adjusting Nyquist limit and colour gain settings in every incidence to optimize the colour Doppler flow signal. From the apical window, the pulsed Doppler sample volume was placed at the mitral valve tips. Right ventricular diameter, as well as right atrial diameter was determined in the apical 4-chamber view. Measuring tricuspid annular plane systolic excursion on M-mode echocardiography assessed right ventricular function at rest.

At rest as well as at every stage during exercise, right ventricular cardiac output was calculated from the flow velocity time integral in the right ventricular outflow tract obtained by pulsed wave Doppler echocardiography. When performing Doppler tissue imaging, filters were set to exclude high frequency signals and from the apical 4-chamber view, a 5 mm sample volume was placed at the lateral corner of the mitral annulus. To evaluate diastolic function and elevation of left atrial pressure, e' lower than 15 cm/sec and E/e' higher than 8 was considered as impaired relaxation.[16] Tricuspid valve regurgitant gradient was calculated from tricuspid regurgitant velocities obtained by continuous Doppler echocardiography using the simplified Bernoulli equation (4 times velocity squared). Right atrial pressure was assumed 5 mmHg as patients had no clinical symptoms of heart failure. Pulmonary artery systolic pressure was subsequently calculated as the sum of the tricuspid valve regurgitant gradient + 5 mmHg. Tricuspid valve regurgitant velocity was measured with contrast enhancement using agitated geloplasma, as previously validated at rest and during exercise.[17-19]

Pulmonary vascular resistance (PVR) was calculated from the equation: (mean PAP – left atrial pressure) / cardiac output. Mean pulmonary artery pressure was calculated from pulmonary artery systolic pressure (0.61 times PASP + 2).[20] Left atrial pressure was calculated from the equation: 1.91 + 1.24*(E/e').[21]

Cardio-pulmonary Exercise Testing:

All participants underwent a symptom-limited, incremental cardio-pulmonary exercise test on a supine bicycle ergometer (Ergometrics, 800S, Ergometrics, Bitz, Germany). The initial workload of 20W was increased by 20W every minute until exhaustion. Twelve-lead ECG monitoring (Max Personal Exercise Testing, Marquette, WI), blood pressure monitoring and gas exchange measurements were

performed in all participants. Respiratory data were collected continuously by breath-by-breath analysis (Oxygen AlphaR, Jaeger, Mijnhardt, Bunnik, The Netherlands). The Gas-exchange analyser was calibrated before each test. Oxygen and carbon dioxide concentration were continuously measured in the inspired and expired air to determine oxygen uptake (VO_2) and carbon dioxide output (VCO_2). Peak oxygen consumption (peakVO_2) was defined as the highest 30s-average of oxygen uptake at the end of the test. Respiratory gas exchange ratio (RER) was calculated as carbon dioxide output divided by oxygen uptake (VCO2/VO2).

Data analysis

Patients were divided into two groups for comparison according to tricuspid insufficiency severity on resting echocardiography. One group consisted of patients with no or minimal tricuspid insufficiency, graded as ≤1/4 on semi-quantitative colour Doppler flow echocardiography. The second group consisted of patients with mild tricuspid insufficiency graded 2/4.

Continuous data are presented as mean ± SD. Categorical data are presented as frequencies and percentages. Normality was assessed using the Shapiro-Wilk test of Normality. The criteria for normality were not met for mean pulmonary artery pressure at rest ($p=0.035$) and at peak exercise ($p=0.016$) as well as for tricuspid valve insufficiency severity ($p<0.001$). Mann-Whitney U non-parametric test or Fishers exact test were performed where appropriate.

All tests were two-tailed. $p<0.05$ was considered significant. Statistical analysis was performed using SPSS®(version 19, SPSS, Chicago).

Results

Patient characteristics

Twenty-seven patients with percutaneous closed atrial septal defect were retrieved for analysis. Two patients were excluded. In 1 patient, resting tricuspid regurgitant velocities could not be obtained, not in rest or at peak exercise. In another patient no tricuspid regurgitant velocities could be obtained at peak exercise. Data analysis was performed on the remaining 25 patients, mean age 42 ± 17 years. Demographic and clinical characteristics are listed in Table 1. There was a female predominance in our

study sample. Patients with persistent mild tricuspid insufficiency were significantly *older* than patients with no or minimal tricuspid insufficiency (p=0.042). There was no statistical difference between the two groups regarding the *age at repair*, although a trend can be assumed (p=0.065). Mean blood pressure, usage of calcium channel blockers and beta-blockade, body mass index and NT-pro BNP levels did not differ significantly between the 2 groups. **(Table 1)**

Echocardiographic variables at rest and at peak exercise

At rest, no significant differences were found for right ventricular diameter, right ventricular diastolic area, right atrial diameter, mean pulmonary artery pressure, right ventricular function as assessed by tricuspid annular plane systolic excursion or right ventricular cardiac output **(Table 2)**. Further, there was no significant difference between the proportions of patients who presented with impaired relaxation of the left ventricle as assessed by e' en E/e' **(Table 2)**. Calculated PVR did not differ significantly between groups.

Table 1 Demographic and clinical characteristics.

		Total	**TI ≤1/4**	**TI 2/4**	**P value**
Total patients	N	25	19	6	
Gender (male)	N (%)	6 (24)	6 (31.6)	0 (0)	0.278
Age (y)	Mean (±SD)	42 (17)	38 (15)	53 (18)	0.042*
Age at repair (y)	Mean (±SD)	34 (21)	30 (18)	47 (23)	0.065
CCB	N (%)	0 (0)	0 (0)	0 (0)	--
Beta blocker	N (%)	9 (36.0)	6 (31.6)	3 (50)	0.630
NT pro-BNP (ng/l)	Mean (±SD)	111 (80)	94 (64)	168 (97)	0.086
BMI	Mean (±SD)	26 (5)	25 (6)	27 (2)	0.127

CCB: calcium channel blocker, BMI: body mass index; NT pro-BNP: NT pro natriuretic peptide

At peak exercise, *mean pulmonary artery pressure* was significantly higher in patients with mild TI compared to those with minimal TI (p=0.026). The evolution of mean pulmonary artery pressure during exercise is shown in Figure 1. The change in right ventricular cardiac output or in mean blood pressure did not differ significantly between the 2 groups at peak exercise **(Table 2)**. E/e' and e' at peak exercise could be obtained in 18/25 patients. There was no significant difference in the prevalence of impaired relaxation between both patient groups **(Table 2)**.

Maximal exercise performance and severity of tricuspid insufficiency

Peak oxygen uptake was significantly lower if mild persistent tricuspid insufficiency was present (p=0.019), however, no significant difference between the 2 groups was found when peak oxygen uptake was expressed as percentage of sedentary values. Furthermore, no significant differences concerning anaerobic threshold, respiratory gas exchange ratio or peak oxygen pulse were found **(Table 3 and Figure 2)**.

Figure 1 Evolution of mean PAP during exercise. Results are presented as means, error bars delineate standard deviation. (p<0.05 = significant)

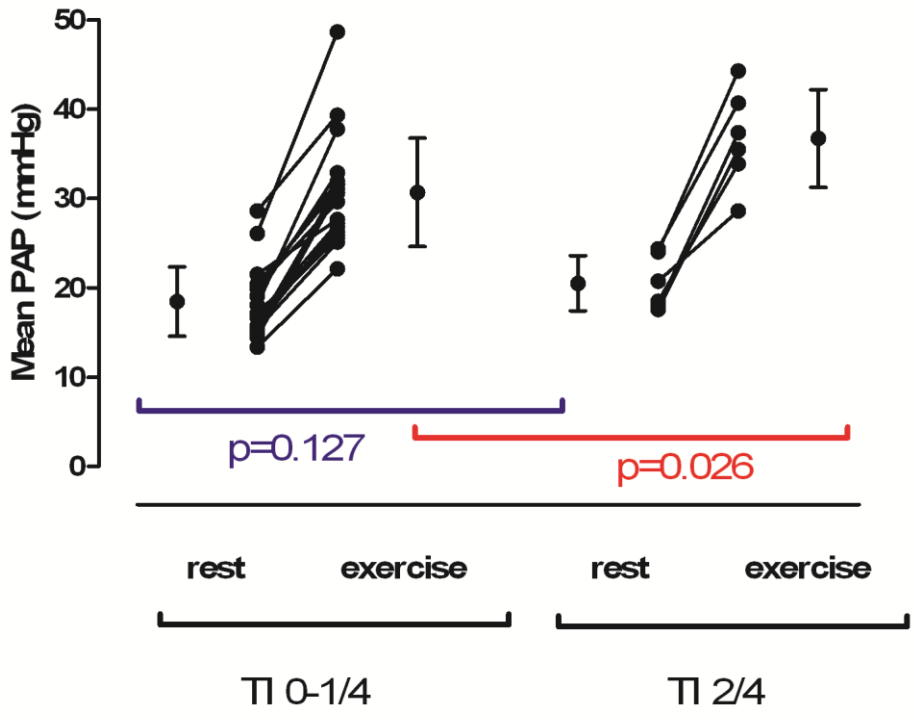


Table 2 Echocardiographic parameters at rest and at peak exercise.

		Total	**TI ≤1/4**	**TI 2/4**	**P value**
Values at rest					
MI 0/4	N (%)	15 (60%)	13 (68.4%)	2 (33.3%)	0.178
1/4		6 (24%)	3 (15.8 %)	3 (50%)	
2/4		4 (16%)	3 (15.8 %)	1 (16.7%)	
Mean BP (mmHg)	Mean (±SD)	88.4 (10.2)	87.1 (9.9)	92.7 (11)	0.203
RV diameter (mm)	Mean (±SD)	31.6 (6.8)	32.0 (7.7)	30.1 (2.8)	0.949
RV area diast (cm^2)	Mean (±SD)	23.49 (5.5)	23.53 (6.14)	23.38 (3.47)	0.889
RA diameter (mm)	Mean (±SD)	45.3 (5.4)	45.1 (4.8)	45.9 (7.4)	1.000
TAPSE (mm)	Mean (±SD)	23.6 (5.0)	23.0 (5.3)	25.4 (3.7)	0.205
RV CO (L/min)	Mean (±SD)	4.2 (0.9)	4.2 (1.0)	4.1 (0.6)	0.656
E'≤15 (cm/s)	N (%)	13 (52)	8 (42)	5 (83.3)	0.605
E/e' ≥ 8	N (%)	2 (8)	2 (10.5)	0 (0)	0.456
Mean PAP (mmHg)	Mean (±SD)	18.95 (3.76)	18.46 (3.89)	20.51 (3.07)	0.127
PVR (WU)	Mean (±SD)	2.5 (1.1)	2.5 (1.3)	2.5 (1.3)	0.765
Values at exercise					
Mean BP (mmHg)	Mean (±SD)	104.0 (11.2)	104.3 (11.8)	102.8 (10.0)	0.545
RV CO (l/min)	Mean (±SD)	9.8 (2.8)	9.8 (3.2)	9.7 (1.5)	0.944
E'≤15 (cm/s)	N (%)	3 (16.7)	2 (11.1)	1 (5.6)	0.650
E/e' ≥ 8	N (%)	4 (22.2)	2 (11.1)	2 (11.1)	0.299
Mean PAP (mmHg)	Mean (±SD)	32.14 (6.39)	30.69 (6.08)	36.72 (5.46)	0.026*

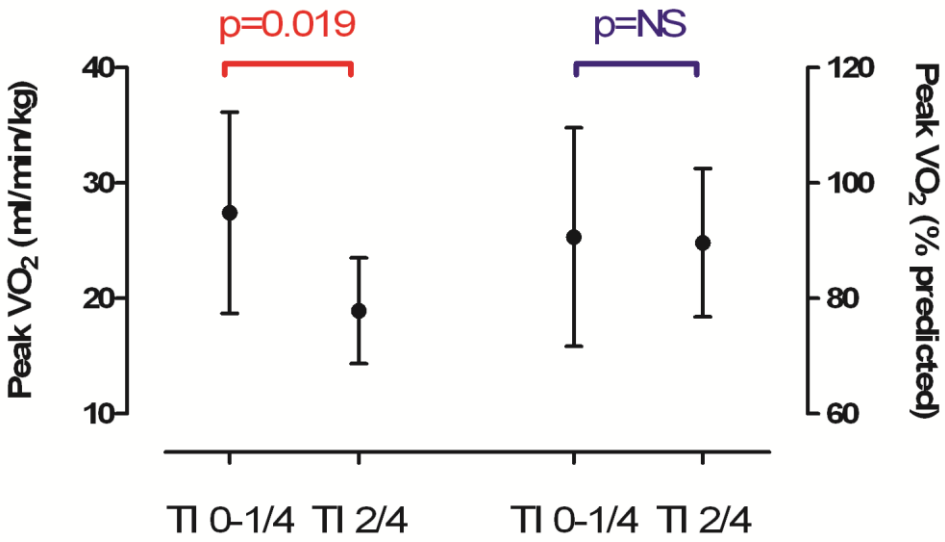
MI: mitral valve insufficiency; BP: blood pressure; RV: right ventricle; TAPSE: tricuspid annular plane systolic excursion; CO: cardiac output; mean PAP= mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; WU: Wood Units.

Table 3 Exercise parameters.

		Total	TI ≤1/4	TI 2/4	P value
Peak VO_2 (ml/kg/min)	Mean (±SD)	25.4 (8.7)	27.4 (8.7)	18.9 (4.6)	0.019*
Peak VO_2 % of predicted	Mean (±SD)	90 (17)	90 (19)	90 (13)	0.774
Peak Oxygen pulse (ml/beat)	Mean (±SD)	11.6 (4.4)	12.2 (4.8)	9.7 (1.9)	0.408
RER	Mean (±SD)	1.14 (0.10)	1.15 (0.10)	1.11 (0.07)	0.390
VE/VCO2 slope	Mean (±SD)	27.1 (1.9)	26.7 (1.7)	28.6 (1.9)	0.026*
Anaerobic threshold (Watt)	Mean (±SD)	104 (65)	115 (71)	73 (27)	0.155

Peak VO_2: peak oxygen consumption; RER=respiratory gas exchange ratio

Figure 2 Peak VO_2 and percentage of predicted peak VO_2. Results are presented as means, error bars delineate standard deviation.



Discussion

This study showed that patients with persistent mild tricuspid tricuspid valve insufficiency (2/4) after atrial septal defect closure are *older*, have a significantly *higher mean pulmonary artery pressure* at peak exercise, and tend to have their atrial septal defect closed at older age, when compared to patients with no or minimal

tricuspid insufficiency (≤ 1/4). Finally, patients with mild tricuspid insufficiency present with a lower maximal oxygen uptake.

Tricuspid insufficiency is a common finding in patients with an atrial septal defect and originates from right ventricular dilatation, tricuspid annulus dilatation, increased pulmonary artery pressure as well as right ventricular dysfunction.[6, 22] Persistent tricuspid insufficiency after atrial septal defect closure has been linked to an increased pulmonary artery pressure at rest.[13] However, even though both right ventricle configuration and pulmonary artery pressure usually normalizes after atrial septal defect closure, persistent mild tricuspid insufficiency is often encountered.[9-14, 22, 23] This is also shown in our series.

Persistent mild tricuspid valve insufficiency is age-related

Patients who present with persistent mild tricuspid insufficiency after atrial septal defect closure are older than those with no or minimal tricuspid insufficiency. However, no significant relation between tricuspid insufficiency severity and late closure of the atrial septal defect was found, although a trend can be assumed. It can be hypothesized that the combination of age-related valve degeneration and a longer standing volume load by the presence of an atrial septal defect, interferes with the geometry of the tricuspid valve and, therefore, increases the age-related prevalence of tricuspid insufficiency. Moreover studies have indicated that if an atrial septal defect is closed after the age of 25 years, the mortality is slightly higher than in healthy controls with a 10 year survival of 90 % compared to 98 % respectively.[24] This suggests that some processes in the right heart circulation are altered, including the development of tricuspid insufficiency, and lead to changes in outcome.

Persistent mild tricuspid insufficiency is associated with higher mean pulmonary artery pressure at exercise

We questioned why a different degree of tricuspid insufficiency was found in patients after atrial septal defect closure, although the morphological and functional characteristics of the right heart were similar between patients with mild and patients with minimal tricuspid insufficiency. However, at exercise there was a significant difference in mean pulmonary artery pressure between the patients that presented with persistent mild tricuspid insufficiency and those with no or minimal tricuspid insufficiency. It is known that in patients who underwent closure of the atrial septal

defect at older age, pulmonary artery pressure increases more during exercise compared to patients who underwent early closure.[15] Additionally, we could now identify an association between persistent mild tricuspid insufficiency (2/4) and increased mean pulmonary artery pressure during exercise. This additional pressure-load on the right ventricle during exercise might be a contributing factor to the persistence of tricuspid insufficiency after atrial septal defect closure maintaining subtle changes in right ventricular geometry, the valvular apparatus or the cardiac cytoskeleton.

Reason for higher meanPAP at peak exercise

The higher mean PAP at peak exercise could be explained by 2 mechanisms. First, long-standing volume-overload of the right ventricle as caused by an open atrial septal defect induces alterations in the histology of the pulmonary vasculature as well as pulmonary arterial vasoconstriction.[25-27] Endothelial damage due to chronic pulmonary arterial congestion induces endothelial dysfunction, degradation of the extracellular matrix and inflammation of the pulmonary arterioles as well as the release of growth factors eventually leading to pulmonary hypertension.[28-30] After atrial septal defect closure, these changes cause persistent elevated pulmonary artery pressure in some patients.[28, 31] However, if these changes are minimal, pulmonary vascular resistance and consequently pulmonary artery pressure are normal at rest. When an exercise is initiated, the pulmonary vascular bed normally responds to this with lowering the pulmonary vascular resistance.[32] If subclinical changes of the pulmonary vasculature have occurred, this decrease in pulmonary vascular resistance does not occur, leading to a larger increase in pulmonary artery pressure at peak exercise. On the other hand, age has been shown to be associated with higher pulmonary artery pressures at peak exercise.[33] in the studied population; patients who presented with mild persistent TI were significantly older than those with TI $\leq$ 1/4. This fits with the higher meanPAP at peak exercise.

Persistent mild tricuspid insufficiency is associated with a lower peak oxygen uptake

Increasing severity of tricuspid insufficiency has an impact on the prognosis of patients.[7] In patients with a closed atrial septal defect, persistent tricuspid insufficiency is associated with increased cardiovascular morbidity and mortality.[6, 13] In our series, patients with persistent mild tricuspid insufficiency had a significantly

lower peak oxygen uptake than patients with minimal or no tricuspid insufficiency, however, if peak oxygen uptake was expressed as a percentage of predicted peak oxygen uptake, no significant difference between groups was found. Other measures for exercise capacity or stroke volume were not significantly different either. Peak oxygen uptake is mainly determined by cardiac output (VO_2=Cardiac Output * arteriovenous oxygen difference) and is age-dependent.[34] The difference in peak oxygen uptake might therefore be solely attributed to the age difference between the 2 groups. Nevertheless, lower pump efficiency caused by more severe tricuspid insufficiency, subclinical myocardial dysfunction as well as increased pulmonary artery pressure during exercise could lead to lower values for peak oxygen uptake. Possibly, in our series, the increase in mean pulmonary artery pressure at exercise causes only structural changes at the level of the right ventricle that lead to tricuspid insufficiency. The severity of tricuspid insufficiency however does not seem to influence exercise capacity. Most likely, tricuspid insufficiency in our studied population was not severe enough to see differences on cardio-pulmonary exercise testing. Unfortunately, the impact of more than mild tricuspid insufficiency could not be assessed from our dataset.

Prognosis in patients after atrial septal defect closure

Prognosis in patients who underwent atrial septal defect closure is good.[24] Improving prognosis in patients who had late closure of an atrial septal defect remains difficult. A possible point of action might be the volume-overload of the right ventricle caused by persistent tricuspid insufficiency. Decreasing pulmonary artery pressure by targeted vasodilator therapy causes a reduction of tricuspid insufficiency severity.[35] A possible therapeutic option in patients with mild persistent tricuspid insufficiency and increased pulmonary artery pressure during exercise could therefore be pulmonary specific vasodilator therapy. This could eventually lead to a decreased volume-overload of the right ventricle, longer preservation of right ventricular function and improvement of functional capacity and prognosis.

Study limitations

This study has several limitations. Tricuspid insufficiency severity was graded semi-quantitatively using colour Doppler flow echocardiography. During exercise, tricuspid insufficiency severity was not assessed. Patients with mild tricuspid insufficiency

were all female. However, although pulmonary artery systolic pressure at rest tends to be higher in females, studies have indicated that pulmonary artery systolic pressure at peak exercise is significantly higher in men than in women.[14, 36] Next, tricuspid insufficiency 2/4 is currently not considered as pathological and most patients did not exhibit mean pulmonary artery pressure at peak exercise that are considered to be pathological.[37] However, we did not want to identify exercise-induced pulmonary hypertension but wanted to assess differences in loading of the right ventricle as a cause of persistent mild tricuspid insufficiency. Further, analysis could be underpowered due to the small sample size. Last, these findings are based on descriptive statistics. A causative relation can thus only be hypothesized.

Conclusion

Persistent mild tricuspid insufficiency after atrial septal defect closure is common in clinical practice. A larger increase of pulmonary artery pressure during exercise could be the pathophysiological mechanism by which mild tricuspid insufficiency persists. However, further study is needed to confirm this hypothesis.

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2. Functional and hemodynamic assessment of mild to moderate pulmonary valve stenosis at rest and during exercise.

Abstract

Objective

In adult patients with mild to moderate pulmonary valve (PV) stenosis, exercise capacity and hemodynamics have not been extensively studied although regular exercise is recommended. Therefore, we aimed to assess exercise capacity, to study the increase in PV gradient during exercise, and to evaluate the impact of this increased pressure-load on the right ventricle.

Methods

Nineteen patients (8 female; 29±6.4 years) with isolated mild to moderate PV stenosis and no prior cardiac interventions were consecutively enrolled from the outpatient clinic of adult congenital heart disease. All patients underwent cardio-pulmonary exercise testing, transthoracic echocardiography and bicycle stress echocardiography. Results for exercise testing were compared to age and gender matched control patients.

Results

In the studied population, resting heart rate (89±11 vs. 75±14bpm; p=0.001), peak power (199±66 vs. 263±68Watt; p=0.006); peak VO2 (31.2±9.9 vs. 39±7.4ml/kg/min; p=0.011); Oxygen Uptake Efficiency Slope (2430±913 vs. 3292±943(ml/min)/(l/min); p=0.007) and VE/VCO2 slope (26.8±5.2 vs. 22.6±4.3; p=0.01) differed significantly from controls. A linear increase of peak PV gradient with increasing flow was observed in the pooled dataset (Pearson's R=0.947; p<0.0001) and slopes identical as for control patients were obtained for the oxygen pulse–workload relationship. Right heart morphology and function were preserved in the studied patients.

Conclusions

Patients with mild to moderate PV stenosis have decreased exercise capacity. A linear increase in PV gradient with flow suggests a fixed valve area throughout the exercise. Although systolic RV pressure load increases during exercise, good ventricular performance was observed without signs of functional or morphological changes of the right heart.

Introduction

Pulmonary valve stenosis occurs in 1 per 2000 live births and accounts for 8% of all congenital heart defects. In 80-90 % of cases, the valve is dome-shaped with a pinhole orifice and no or incomplete separation of the leaflets. Rarely, the malformation consists of thickened valve leaflets with commissural fusion or pulmonary valve dysplasia.[1, 2, 3] Evaluation of severity of stenosis is made by Doppler echocardiography with a transvalvular gradient <36 mmHg, between 36-64 mmHg and >64 mmHg considered as mild, moderate and severe pulmonary valve stenosis respectively.[4]

In cases of severe outflow tract obstruction, infundibular hypertrophy and small subendocardial infarctions in the right ventricular free wall and papillary muscles can occur. Consequently, exercise capacity is reduced due to an inability to increase stroke volume with the increase in heart rate being the sole contributor to an increase in cardiac output.[5, 6] Conversely, the natural evolution of mild pulmonary valve (PV) stenosis is considered to be benign without progression of the valve gradient after adolescence and no deaths are observed during an 8-year follow-up period.[3, 7] Because of this, no restrictions in physical activity are imposed.[8, 9]

However, the exercise capacity and hemodynamics of patients with mild to moderate PV stenosis have not been investigated thoroughly. Although the defect is simple, the increase in valvular gradient at peak exercise and its impact on exercise performance has hardly been investigated. Romeih et al. made a first attempt to investigate the mechanisms underlying possible impairment of the exercise capacity in patients with moderate PS. They demonstrated in a small group of asymptomatic patients with native moderate PS that the exercise capacity and cardiac reserve remained normal.[10]

However, their evaluation of cardiac function was based on pharmacological stress, rather than physical stress and the impact on pulmonary valve and right ventricular function was not documented.

Therefore, we wanted to assess exercise capacity in patients with mild to moderate PV stenosis, to study the increase in pulmonary valve gradient with increasing cardiac output, and to evaluate the impact of the pressure-load at peak exercise on the right ventricle.

Methods

Patient selection and data collection

From 18 October 2011 until 24 May 2013, consecutive patients were included from the outpatient clinic of congenital heart disease at the University Hospital of Leuven. Patients with isolated mild to moderate pulmonary valve stenosis, as evidenced by a PV Doppler gradient <64mmHg and no prior cardiac interventions were eligible for inclusion in the study. Exclusion criteria were age under 16 years and contra-indication for exercise testing. Furthermore, patients with known coronary artery disease, significant valvular disease other than pulmonary regurgitation (>1/4), associated cardiac malformations and a history of arrhythmias or current arrhythmias were excluded from the study. Patients with Noonan's syndrome or other chromosomal abnormalities were excluded. All patients had the classical form of pulmonary valve stenosis. All patients underwent symptom-limited cardio-pulmonary exercise testing and bicycle stress echocardiography. In all patients informed consent was obtained at inclusion. Approval for patient inclusion and data collection was obtained from the local ethics committee.

Cardio-pulmonary exercise testing

All participants underwent a symptom-limited, incremental cardio-pulmonary exercise test on a bicycle ergometer (Ergometrics, 800S, Ergometrics, Bitz, Germany). Workload was increased by 20 Watts every minute until exhaustion.

Simultaneous gas exchange measurement, 12-lead ECG monitoring (Marquette Max Personal Exercise Testing, WI, USA) and blood pressure monitoring were performed. The oximeter was calibrated before each test. Respiratory data were collected by

breath-by-breath analysis (Oxygen Alpha®, Jaeger, Mijnhardt, Bunnik, The Netherlands) with continuous monitoring of oxygen and carbon dioxide concentrations in the inspired and expired air to determine oxygen uptake (VO2) and carbon dioxide output (VCO2). Peak oxygen consumption (peakVO2) was defined as the highest 30-s average of oxygen uptake at the end of the test. Respiratory gas exchange ratio was calculated as carbon dioxide output divided by oxygen uptake (VCO2/VO2). Anaerobic threshold was determined by the V-slope method. All slopes were calculated after exclusion of the first minute of exercise. The VE/VCO2 slope was calculated by plotting the VCO2 as a function of ventilation. The measurements after the respiratory compensation point were omitted. The oxygen uptake efficiency slope (OUES) was calculated by plotting the VO2 as a function of the log of ventilation. VO2 was plotted as a function of work rate resulting into the VO2/WR relationship. Oxygen pulse was calculated as the VO2 divided by heart rate.[11]

Control population

To compare the gas-exchange parameters of the patient population, a control population was selected from the database of cardio-pulmonary exercise testing at the university hospitals of Leuven by 1:1 age and gender matching. Matching was automated by using the "Fuzzy" extension command as available from the SPSS website (www.ibm.com). Parameters were set to obtain exact matches.

Transthoracic echocardiography and bicycle stress echocardiography

All patients underwent a standard transthoracic echocardiographic examination. All examinations were performed on a Vivid 9 ultrasound system (General Electric Vingmed Ultrasound, Horten, Norway) equipped with a 3 Mhz probe. Exercise echocardiography was performed on a semi-supine ergometer tilted laterally from 20° to 30° to the left (Easystress, Ecogito, Medical sprl, Liège, Belgium). The protocol started at 25 watts with an increment of 25 watts every 2 minutes until the maximum tolerated load.

A single observer performed the measurements. All measurements were made in triplicate and averaged for analysis. Analysis was done off-line using dedicated software (EchoPac, Genereral Electric Vingmed Ultrasound, Horten, Norway).

In all patients, a complete resting echocardiographic study was performed in the supine position. All Doppler echocardiographic and tissue Doppler imaging record-

ings were obtained during normal respiration. At rest, valvular insufficiency of the atrioventricular valves was evaluated semi-quantitatively by colour Doppler flow mapping and valvular stenosis was evaluated by aligning the continuous wave Doppler beam with the studied valve. The highest velocities obtained were included for analysis and the pressure gradient was calculated from the simplified Bernoulli equation. From the apical window, the pulsed Doppler sample volume was placed at the tips of the mitral valve to evaluate the mitral valve inflow pattern. Also, right ventricular area was measured at end-diastole and end-systole from a RV focused apical 4-chamber view. Right atrium area was measured from the 4-chamber view at end-systole. Right ventricular function was evaluated by measuring the tricuspid annular plane systolic excursion (TAPSE) on M-mode echocardiography and fractional area change (FAC = (end-diastolic area – end-systolic area) / end-diastolic area) at rest from a RV focused apical 4-chamber view.

At rest as well as at every stage during exercise, cardiac output and PV gradient were obtained. Cardiac output was calculated from the flow velocity time integral in the left ventricular outflow tract obtained by pulsed wave Doppler echocardiography. The left ventricular outflow tract diameter was measured at rest and assumed constant throughout exercise. PV velocities were measured by aligning the CW Doppler beam along the PV and the pressure gradient was subsequently calculated. TR severity was assessed by colour Doppler echocardiography and graded semi-quantitatively from 0-4/4.

Statistical Analysis

Data of continuous variables are presented as means ± standard deviation and categorical variables as frequencies and percentages.

Demographic and exercise parameters of the study and control population were evaluated using the independent student t-test and chi-square test where appropriate.

Pearson’s correlation coefficient was calculated for resting pulmonary valve gradient and pulmonary valve gradient at peak exercise in each subject. Pearson’s correlation coefficient for cardiac output and PV gradient was calculated on the pooled measurements of all patients and every stage of exercise. Furthermore, the slope of the O2pulse–workload relationship of patients was compared to that of controls. To

allow for analysis of the pooled data and account for the inter-subject variability, Poon recalibration of the data was performed.[12]

All tests were two-tailed. A P-value <0.05 was considered significant. Analyses were performed using SPSS® (version 22 SPSS, Chicago, USA).

Results

Patient characteristics

Nineteen patients with PV stenosis, 8 (42%) female, aged 29 ± 6.4 years, were included in the study. None of the patients had known chromosomal abnormalities and all were diagnosed with the classic form of PV stenosis. Demographic data can be found in **Table 1**.

Table 1 Demographics of patients with pulmonary valve stenosis and healthy controls. Patients are compared using an independent student t-test or *chi^2 test where applicable; p<0.05=significant.

			Patients		**Controls**	
		N		N		P-value
Gender	N female (%)	19	8 (42)	19	8 (42)	1*
Age (yrs.)	Mean ± SD	19	29 ± 6.4	19	29 ± 6.4	1
Height (cm.)	Mean ± SD	19	174 ± 9	19	177 ± 12	0.33
Weight (kg.)	Mean ± SD	19	74.6 ± 15.6	19	74.6 ± 12.3	0.993
BMI (kg/m^2)	Mean ± SD	19	24.6 ± 4.7	19	23.8 ± 3.5	0.538
BSA (m^2)	Mean ± SD	19	1.9 ± 0.2	19	1.9 ± 0.2	0.704
Heart rate (bpm)	Mean ± SD	19	89 ± 11	19	75 ± 14	0.001
Systolic BP (mmHg)	Mean ± SD	19	122 ± 13	19	133 ± 18	0.049

BMI= body mass index; BSA=body surface area; BP=blood pressure.

Cardio-pulmonary exercise test

All patients performed a cardio-pulmonary exercise test at near maximal levels as evidenced by respiratory exchange ratio of 1.2 ± 0.08 in the patient population, 1.2 ± 0.07 in the control population (p=0.067).

In the studied patient population, heart rate increased from 89bpm ± 11 to 181bpm ± 11. Resting heart rate was significantly higher in the patient population compared with age and gender matched controls (89 ± 11 vs. 75 ± 17 bpm; p=0.001). Heart rate reserve was significantly lower in the patient population ((92 ± 16 vs. 110 ± 21 bpm; p=0.007). (Figure 1) However, peak HR was not different compared to controls (181 ± 11 vs. 187 ± 17 bpm; p=0.5).

Compared with controls, patients with PV stenosis presented with significantly lower exercise capacity as evidenced by a lower peak power (199 ± 66 vs. 263 ± 68 Watt; p=0.006); peak VO2 (31.2 ± 9.9 vs. 39 ± 7.4 ml/kg/min; p=0.011) and power at anaerobic threshold (83 ± 34 vs. 146 ± 41 Watt; p<0.0001). **(Figure 1)**

Furthermore, patients had evidence of lower ventilatory efficiency as shown by a significantly lower OUES (2430 ± 913 vs. 3292 ± 943 (ml/min)/(l/min); p=0.007) and higher VE/VCO slope (26.8 ± 5.2 vs. 22.6 ± 4.3; p=0.01). (Figure 1) No significant difference in peak oxygen pulse (14.66 ± 4.3 vs. 15.98 ± 4.31; p=0.351) or in VO2/WR relationship (9.47 ± 1.18 vs. 9.73 ± 1.13; p=0.491) was observed.

Lastly, the slope of the oxygen pulse as function of increasing workload didn't differ between the patient population and the control population (y=0.039x+6.72 and 0.040x+5.61 respectively; p=0.525). **(Figure 2)**

Stress echocardiography

Mean power at peak exercise for semi-supine bicycle stress echocardiography was 146 Watt ± 47. The echocardiographic parameters at rest and during exercise of the PV stenosis patients can be found in Table 2. Left ventricular ejection fraction was 68% ± 9%. None of the patients had signs of left ventricular diastolic dysfunction. Peak gradient across the pulmonary valve was 24 mmHg ± 12 at rest and increased to 54 mmHg ± 22 at peak exercise. Cardiac output increased from 5.1 L/min ± 1.09 to 12.4 L/min ± 3.2. Maximal gradient across the pulmonary valve correlated strongly with resting pulmonary gradient (Pearson's R=0.905; p<0.0001). **(Figure 3)**

Evaluation of linearity of the pooled data showed a strong correlation between cardiac output and PV gradient (y=4.162x-2.463; Pearson's R=0.947; p<0.0001). **(Figure 4)**

PV gradient at rest and at peak exercise respectively didn't correlate with peak cardiac output (R=-0.068; p=0.781 and R=0.212; p=0.480), peak stroke volume (R=-0.177; p=0.469 and R=0.051; p=0.835), TAPSE at rest (R=-0.086; p=0.727 and R=0.001; p=0.407) and RV fractional area change at rest (R=-0.282; p=0.257 and R=-0.208; p=0.407). Furthermore, no correlation was found for PV gradient at rest and at peak exercise for right atrial area (R=0.084; p=0.739 and R=0.336; p=0.173), RV diastolic area (R=0.253; p=0.331 and R=0.368; p=0.133) and RV systolic area (R=0.292; p=0.239 and R=0.362; p=0.140). No assessable increase in TR severity was seen throughout exercise. **(Figure 5)**

Table 2 Echocardiography at rest and at peak exercise in the patient group.

	Rest	**Peak exercise**
	Mean ± SD	Mean ± SD
Pulmonary valve gradient (mmHg)	24 ± 12	54 ± 22
Stroke volume (ml)	69 ± 14	90 ± 19
Cardiac output (L/min)	5.1 ± 1.09	12.4 ± 3.2
Cardiac index (L/min/m^2)	2.7 ± 0.6	6.5 ± 1.3
LV ejection fraction (%)	68 ± 9	
Mitral inflow E velocity (cm/sec)	0.61 ± 0.14	
Mitral inflow A velocity (cm/sec)	0.53 ± 0.12	
Lateral mitral annulus E' velocity (cm/sec)	0.12 ± 0.02	
E/E'	4.12 ± 1.25	
RV fractional area change	0.40 ± 0.07	
TAPSE (cm)	2.3 ± 0.3	
RV area at diastole (cm^2)	19.58 ± 4.76	
RV area at systole (cm^2)	11.78 ± 3.70	
RA area at systole (cm^2)	15.02 ± 3.49	

LV=left ventricle; RV=right ventricle; TAPSE=tricuspid annular plane systolic excursion.

Figure 1 Comparison of exercise parameters for patients with pulmonary valve stenosis and the age and gender matched control population. (A) Evaluation of heart rate at rest, peak exercise and the resultant heart rate reserve (HRR); (B) Peak oxygen uptake (VO2), peak power and power at anaerobic threshold (AT); and (C) Ventilatory efficiency by oxygen uptake efficiency slope (OUES) and ventilation/carbon dioxide output (VE/VCO2) slope.

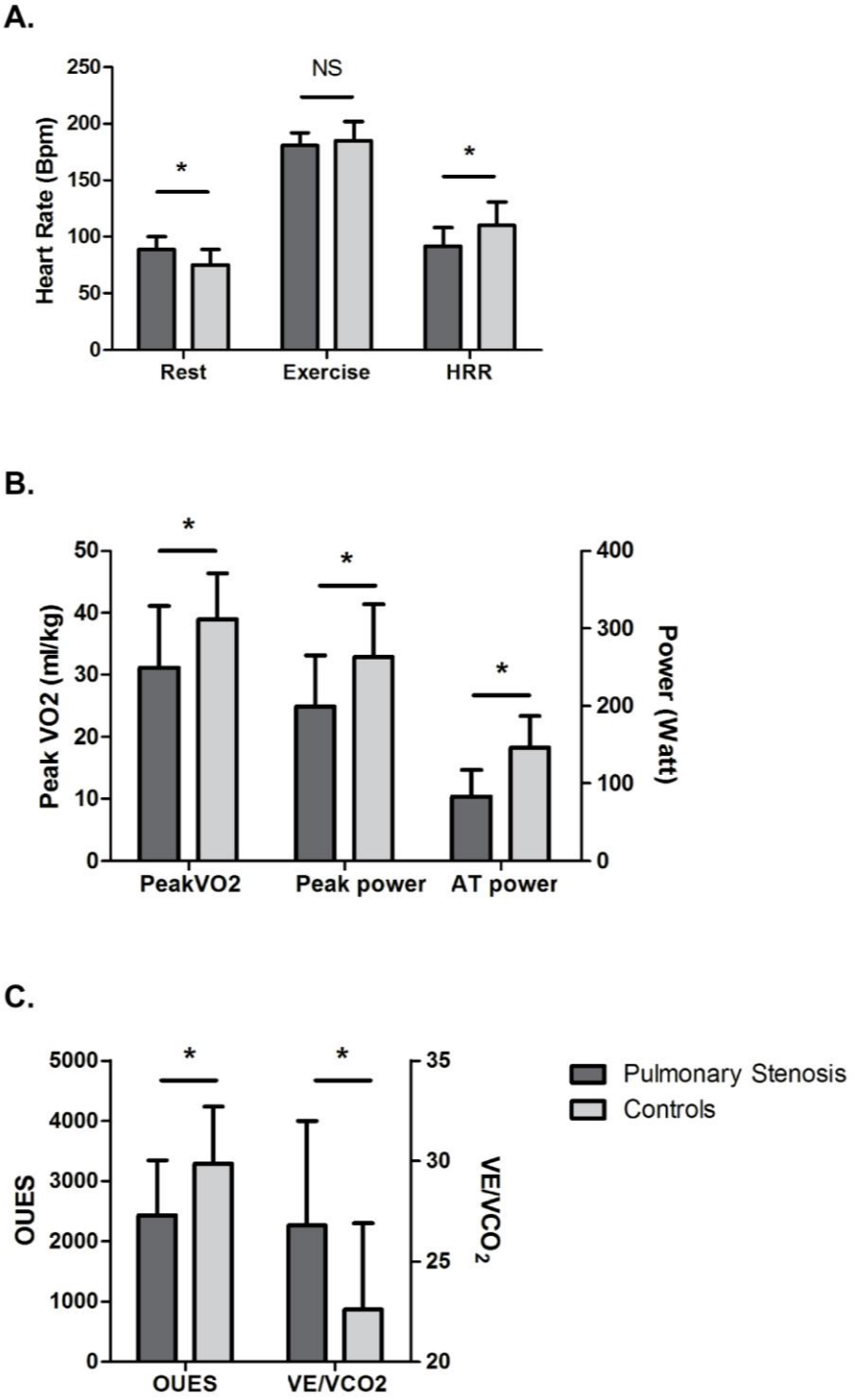


Figure 2 Pooled analysis of all obtained measurements of oxygen pulse as a function of increasing workload. No difference in the slope of the oxygen pulse – workload relationship was found.

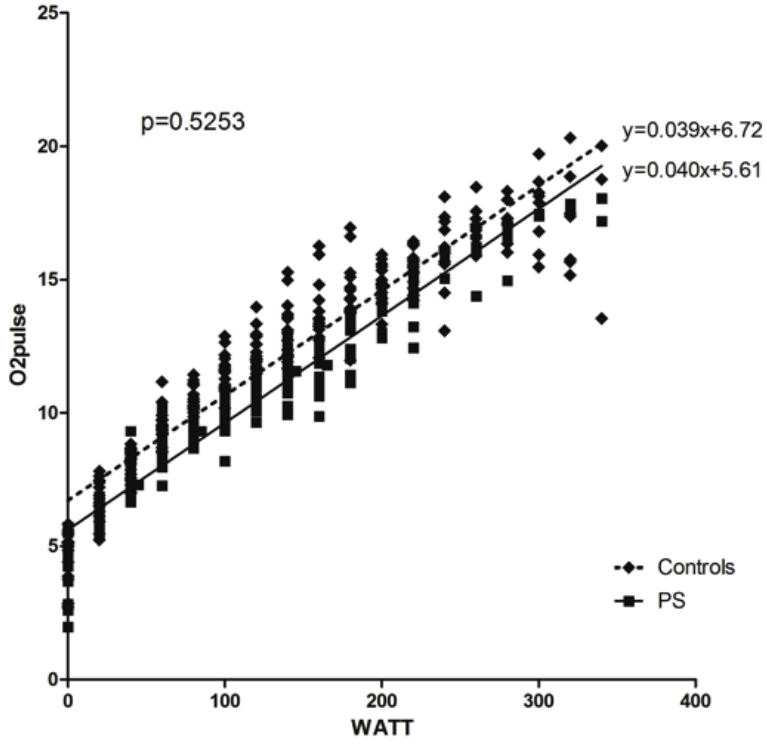


Figure 3 Analysis of pulmonary valve gradient at rest and at peak exercise for all subjects. PV=pulmonary valve.

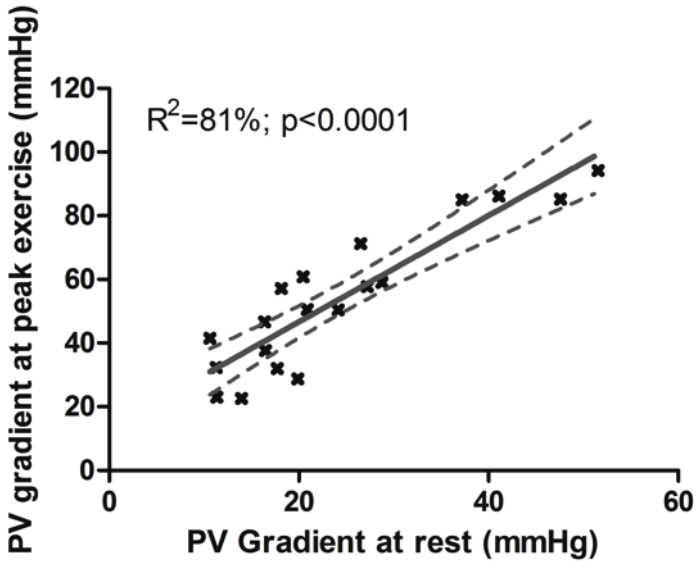


Figure 4 Pooled analysis of all obtained measurement of cardiac output and pulmonary valve gradient during exercise echocardiography.

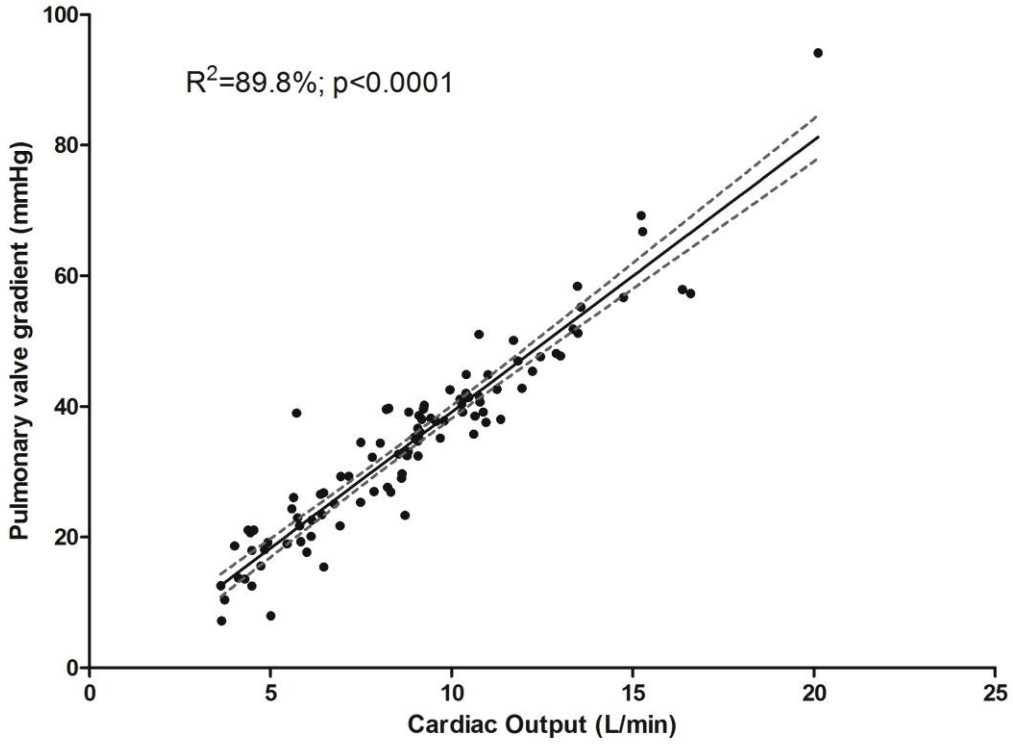
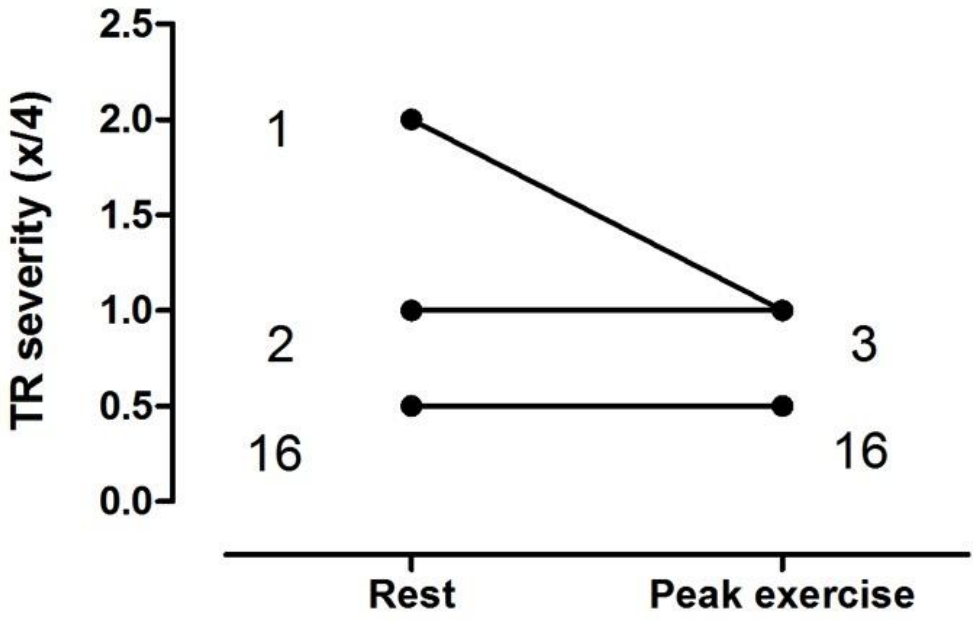


Figure 5 TR severity (X/4) at rest and at peak exercise as assessed by Colour Doppler Echocardiography.



Discussion

This study showed that patients with mild to moderate PV stenosis present with decreased exercise capacity and ventilatory efficiency compared to age and gender matched controls. However, right ventricular performance and right heart morphology was preserved in the studied patients. Lastly, PV gradient increases linearly with increasing flow.

In adult patients with severe PV stenosis, exercise capacity is limited.[5] The hemodynamic response to exercise in patients with mild pulmonary valve stenosis is not well studied. Mild PV stenosis is considered benign and patients can participate in recreational or competitive sports. Adults with moderate pulmonary valve stenosis are subjected to closer follow-up, but when asymptomatic are not limited in moderate recreational sporting activity and should be encouraged to do so.[8, 9]

In our study, only 4 patients had moderate pulmonary valve stenosis. Nevertheless, the studied population presented with a decreased exercise capacity. This in in contrast with Romeih et al. who documented a preserved exercise capacity in 11 patients with moderate PS.[10] Higher resting heart rate, lower heart rate reserve, peak oxygen levels and peak power all point towards a lower physical condition as compared with an age and gender matched control group. Additionally, ventilatory efficiency, i.e. OUES and VE/VCO2 slope, was equally impaired. These are known exercise parameters that are independent from the endpoint of a maximal exercise test, which have shown their value in different heart disease populations.[13, 14, 15] Furthermore, it has been shown that both exercise capacity and ventilatory efficiency improve after relieve of right ventricular pressure load in patients with pulmonary valve stenosis, even if only small improvements of valvular gradient are obtained post-intervention.[16, 17] An increase in afterload reserve and the associated increase in stroke volume at peak exercise is the most likely underlying mechanism.[16] Contradictory to these findings, no significant difference between patients and controls was observed for peak oxygen pulse or for the slope of the oxygen pulse – workload relationship. **(Figure 2)** Both TAPSE and RV fractional area change at rest were within the reference values. These data suggest that stroke volume is not influenced by the presence of mild to moderate PV stenosis. Because our patients were asymptomatic, differences in afterload reserve in our patients with mild to

moderate PV stenosis compared to controls might be less pronounced then in the patient population with more severe obstruction studied by others. Otherwise, in adult patients with only mild PV stenosis, diastolic dysfunction of the right ventricle may contribute to a decreased stroke volume.[6] However, in this study severe diastolic dysfunction was not observed as evidenced by normal right atrial dimensions. Possibly, ventilation-perfusion mismatching due to preferential perfusion of certain regions of the lung might cause impaired ventilatory efficiency. Indeed, depending on the morphology of the valvular stenosis preferential flow to the left or right lung is noticed. Lastly, changes in respiratory function, oxygen delivery or oxygen extraction in the peripheral muscles could contribute as well.

Furthermore, although pressure load of the right ventricle was significantly elevated at peak exercise, no changes in right heart morphology and onset of TR could be seen with increasing maximal pressure load. The pressure load on the right ventricle at peak exercise can be as high as 90 mmHg, well beyond what is considered to be physiological and could be associated with RV dysfunction or arrhythmic problems in the long-term. Patients included in the study were young and the consequences of life-long pressure increase still have to be established. However, at present, our studied population with mild to moderate PV stenosis does not show morphometric changes in the right heart and no assessable increase in TR severity. **(Figure 5)** This is different to what we found in a cohort of patients with pulmonary hypertension where morphometric changes are strongly related with the pressure load on the right heart.[18] This might be because the absolute values of pressure-load in patients with pulmonary hypertension tend to be higher at rest and during exercise compared to our study sample and ventricular function is often impaired in PH patients. Furthermore, in PV stenosis, several factors are thought to contribute to better preservation of right ventricular morphology. The onset, hemodynamic profile and compensatory mechanisms in pulmonary hypertension are very different compared to patients with PV stenosis. In the studied patients, the pressure-load is already present to some extent at birth, it is a purely systolic pressure load and neurohormonal or gene and protein synthesis alterations are thought to play a role in the better preservation of right ventricular morphology and function.[19, 20, 21] To what extent each contributes to this favourable remodelling of the right ventricle has still to be investigated.

In summary, the studied patients presented with a decreased exercise capacity, but

were able to increase their stroke volume similarly to healthy controls. In these patients, the lower exercise capacity is therefore mainly attributable to a lower physical fitness, and probably not directly related to the higher right ventricular afterload. The preservation of right heart morphology and function is reassuring and confirms the current practice not withholding recreational exercise in these patients.[8, 9] Promotion of physical activity seems therefore safe and should be mandatory in routine follow-up. However, long-term effects of this lesion on right heart morphology and function remain uncertain.

Finally, we showed a strong linear relation between PV gradient and cardiac output during exercise. Consequently, the resting PV gradient was predictive for the peak PV gradient and from the pulmonary resting gradient; the maximum pressure load at peak exercise can be calculated ($y=1.669x+13.29$). This linear relationship between pressure and flow indicates again a good ventricular performance. On the other hand this indicates a fairly fixed valve area in patients with the classical form of PV stenosis. The absence of a dynamic component also indicates the absence of infundibular hypertrophy as is seen in patients with severe PV stenosis. Our studied patients with mild to moderate pulmonary valve stenosis do not appear to present with such remodelling. This indicates that, if the PV echocardiographic gradient is only mild to moderately elevated, and if the gradient remains stable throughout follow-up, the pressure-load is well tolerated and early intervention is not indicated.

Conclusion

We showed that patients with mild to moderate PV stenosis do have impaired exercise capacity. In PV stenosis, the valve area is fixed throughout the exercise. At present, we don’t have a reason to exclude patients from recreational sports, as no signs of functional or morphological changes of the right heart were observed in the studied range of valve gradients.

Limitations

Our results are based on a fairly small study sample and the study has been done in a single centre. However, we were able to match the patient population with a well-

established control population. This made useful comparative statistics possible. The number of patients is relatively low for calculating correlations. However, the group of patients is quite homogenous with no outliers. Therefore, we believe that an absence of correlation can be interpreted, however, with careful consideration. Long-term follow-up data are needed to confirm this.

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3. Pilot trial: The impact of right ventricular contractile reserve on tricuspid regurgitation severity in patients with repaired tetralogy of Fallot.

Abstract

Objective

The impact of right ventricular (RV) dysfunction in the pathogenesis of tricuspid regurgitation (TR) is incompletely understood. We aimed (1) to assess RV contractile reserve in patients with repaired tetralogy of Fallot and (2) its relation with TR severity in a pilot trial.

Methods and results

From March until June 2014, 5 patients [all male, median age 24 (range 20-32)] with repaired tetralogy of Fallot, were consecutively included from the outpatient clinic of congenital heart disease and were able to complete the study protocol. All patients had a pulmonary homograft at the level of the RV outflow tract. All patients underwent baseline echocardiography and symptom-limited bicycle stress echocardiography to evaluate the increase in pulmonary valve gradient with increasing flow. Next, low-dose dobutamine stress cardiac magnetic resonance imaging (CMR) was performed to evaluate right ventricular contractile reserve.

Patients performed submaximal on bicycle stress echocardiography with peak heart rate 140 bpm (range 120-142) and peak cardiac output 12 L/min (range 7.4-21). The median of the peak instantaneous pressure gradient across the pulmonary homograft at rest was 46 mmHg (range 12-55 mmHg) and increased to 68 mmHg (range 43-108 mmHg) at peak exercise.

On dobutamine-stress CMR, 4 patients showed a preserved contractile reserve. In 1 patient, a bimodal response was observed with initial increase in RV stroke volume at 10µg/kg/min but decreased stroke volume at 20µg/kg/min dobutamine infusion. Patients had no to only slight TR at baseline (median tricuspid regurgitant fraction 6% (range -3%–15%)). Only the patient with impaired RV contractile reserve showed an

increase in regurgitant fraction from 6% to 41% and 34% at 10µg/kg/ml and 20µg/kg/ml dobutamine infusion respectively.

Conclusions

We observed an increase in tricuspid regurgitant fraction in 1 patient presenting with impaired RV contractile reserve. Although we can't make solid conclusions given the low patient number, these findings hint towards a possible contribution of right ventricular dysfunction in preservation of tricuspid valvular competence.

Introduction

In the general population, tricuspid regurgitation (TR) of any severity occurs in more than 80% of patients, whereas significant TR > 2/4 is observed in only 1%.[1] On the other hand, TR is much more prevalent in many cardiac diseases and is associated with impaired prognosis.[2, 3] Right ventricular (RV) dilatation, tricuspid annular dilatation and increased RV pressure are known determinants of TR.[4, 5, 6] However, neither of these lead invariably to severe TR. Less than severe TR can be observed in patients with a dilated right ventricle or tricuspid annulus or in patients with pulmonary hypertension.[5, 7, 8] RV function has sometimes been suggested as being a key factor in the pathogenesis of TR.[4, 9] Unfortunately, it is often difficult to evaluate the influence of RV function as it occurs often in the presence of RV dilatation and/or in the pressure-loaded RV.

Tetralogy of Fallot is the most common cyanotic congenital heart disease, consisting of a combination of 4 defects: (1) a non-restrictive ventricular septal defect, (2) an overriding aorta, (3) RV outflow tract obstruction and (4) RV hypertrophy. Patients present with cyanosis immediately after birth and complete surgical correction, sometimes as a staged approach to mature the pulmonary circulation, is performed at infancy. Although good long-term outcome is observed in these patients, development of RV outflow tract obstruction and RV failure can occur in follow-up. Furthermore, studies have shown that a subset of patients can present with impaired contractile reserve, as evaluated by low dose dobutamine-stress CMR.[10] This offers the unique opportunity to study the evolution of TR severity in patients with preserved and decreased contractile reserve.

Therefore, we performed a pilot study to evaluate (1) right ventricular contractile reserve in patients with repaired tetralogy of Fallot and (2) to evaluate its impact on tricuspid regurgitant severity.

Methods

Patient selection

From 14 March until 17 June 2014, patients were consecutively included from the outpatient clinic of congenital heart disease. Patients had repaired tetralogy of Fallot, with a pulmonary homograft in the position of the RV outflow tract. Patients had to be older than 18 years with no more than mild pulmonary and/or aortic valve regurgitation. Other exclusion criteria were pregnancy, QRS duration ≥ 180 msec, a history of ventricular tachycardia or ventricular fibrillation, atrial fibrillation, claustrophobia and any contra-indication for CMR, dobutamine infusion or exercise testing. Patients with concomitant left-sided heart failure or chronic lung disease were excluded as well. Criteria for discontinuation of the study were significant discomfort of the patient, heart rate > 75% of predicted (220-age) or dysrhythmia.

The ethics committee approved patient inclusion and data analysis.

Baseline echocardiography and bicycle stress echocardiography

Baseline transthoracic echocardiography and bicycle stress echocardiography were performed in all patients. All examinations were done on a Vivid 9 ultrasound system (General Electric Vingmed Ultrasound, Horten, Norway) with a 3 MHz probe. Symptom-limited bicycle stress echocardiography was performed in the semi-supine position, with the ergometer (Easystress, Ecogito, Medical sprl, Liège, Belgium) tilted laterally from 20°-30° to the left. An initial load of 25 Watts was increased with 25 Watts every 2 minutes until the maximum tolerated load.

RV morphologic and functional parameters were obtained at baseline from a RV focused apical four-chamber view, with measurement of the RV area at end-diastole and end-systole. Fractional area change [FAC=(end-diastolic area – end-systolic area)/end-diastolic area] was calculated from these values. Furthermore, tricuspid annular plane systolic excursion (TAPSE) was evaluated on M-mode echocardiography.

Valvular stenosis at rest and during exercise was evaluated by aligning the continuous wave Doppler beam with the studied valve and the highest velocities obtained were used for analysis. From the obtained velocities, the peak instantaneous pressure gradient was calculated from the simplified Bernoulli equation. Cardiac output was calculated from the flow velocity time integral obtained from an apical 5 chamber view by placing the pulsed Doppler sample at the level of the left ventricular outflow tract. The cross-sectional area of the left ventricular outflow tract was derived from baseline measurement of its diameter from a parasternal long-axis view and was assumed constant throughout exercise.

A single observer did data acquisition and analysis. Analysis was done offline using dedicated software (EchoPac, Genereral Electric Vingmed Ultrasound, Horten, Norway). All measurements were made in triplicate and averaged.

Dobutamine-stress cardiac magnetic resonance imaging

All patients were scanned using a 1.5 T MR scanner (Achieva, Philips Medical systems, Best, The Netherlands). Cardiac synchronisation was performed with vector electrocardiography.

- Volumetry

At baseline and during dobutamine infusion, a short axis and long-axis multi-slice volumetric dataset was obtained through a single breathold (9 slices) to cover the ventricles by a 2 dimensional balanced steady state free precession sequence.

Volumetric analysis was repeated at every stage of dobutamine infusion, i.e. at 10 µg/kg/min and at 20 µg/kg/min.

Images were analysed on a software program developed in-house (Right-to–Right Volume Leuven, Leuven, Belgium.[11] In short, end-diastolic and end-systolic frames of each short-axis slice were selected. Each short-axis image was manually traced and the points of transection with the long axis plane were indicated. Trabeculations and papillary muscles were included into the volumes. The contours were used to calculate the volume by the summation of disks method. To take into account interventricular dyssynchrony in patients with repaired tetralogy of Fallot, maximal and minimal volumes were identified separately for the left and the right ventricle, to obtain maximal (and minimal) volumes for each cardiac phase in each ventricle.[12]

Stroke volume was calculated by subtracting end-systolic volume from the end-diastolic volume. Tricuspid valve regurgitant volume was obtained by subtracting left ventricular stroke volume from RV stroke volume. Tricuspid valve regurgitant fraction was calculated by dividing the regurgitant volume*100 by the RV stroke volume.

- Flow quantification

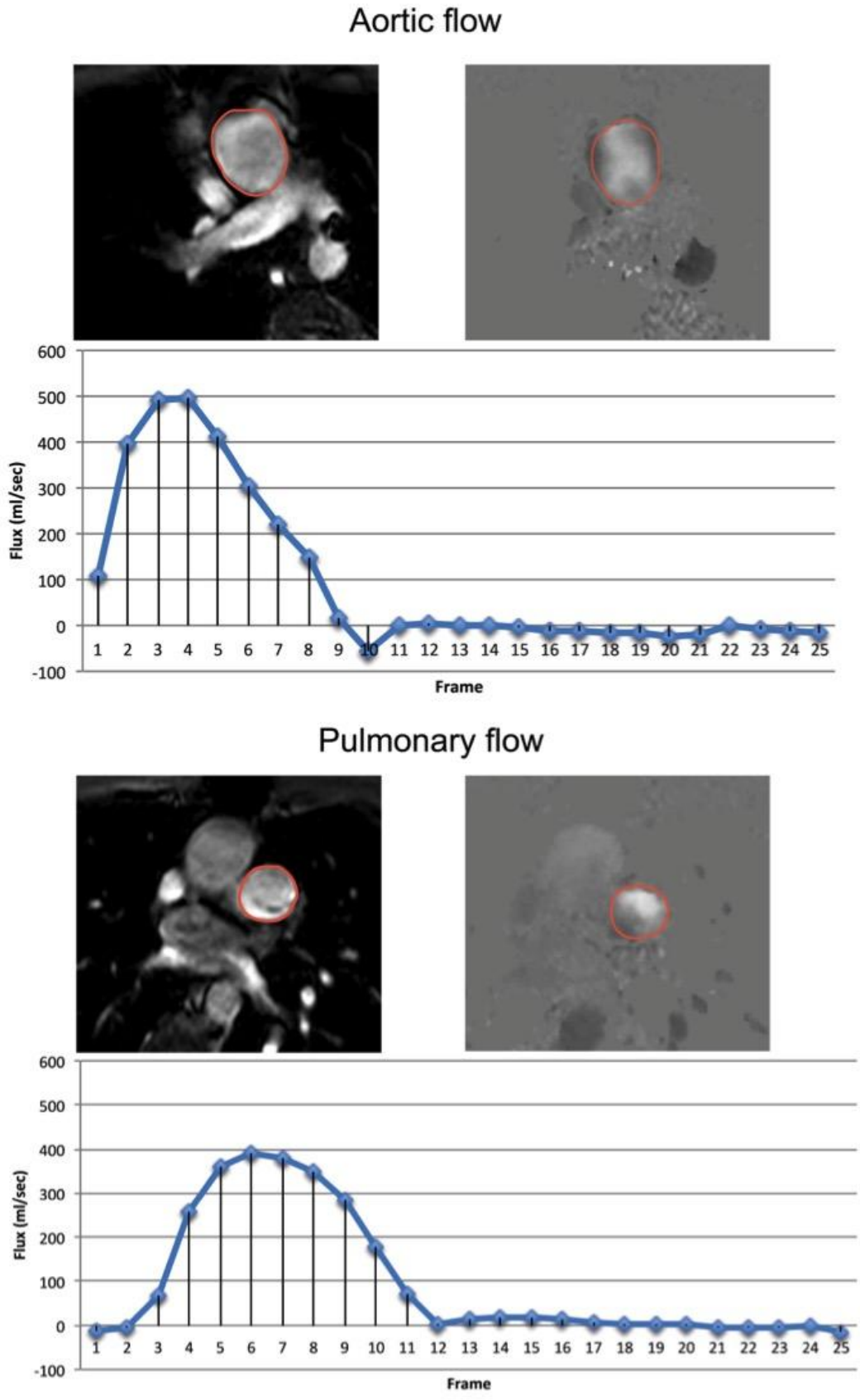
At baseline, pulmonary and aortic regurgitation were evaluated by 2D phase-contrast MRI during free breathing. Image planes were located at the level of the pulmonary and aortic valve respectively.

Flow quantification was performed on dedicated software (QFlow, Philips Healthcare, Best, The Netherlands) in a semi-automated fashion. Contours were traced automatically by the software after selection of the target valve and were manually adjusted frame-by-frame to obtain the best fit.**(Figure 1)** From the obtained flow curves, regurgitant volume and regurgitant fraction were calculated.

Representation of data

Data are represented both graphically as in absolute numbers. Continuous data are represented by medians and minimal-maximal values, categorical data as frequency and percentage. Because of the pilot phase of the study and the small number of patients included, no comparisons between patient's results were performed.

Figure 1 Flow quantification of the aortic and pulmonary valve. Flow was traced in a semi-automatic fashion with manual review and adjustment of each frame.



Results

Patient inclusion

A total of 6 patients were included for analysis. One patient didn't tolerate the dobutamine infusion with significant patient discomfort and hyperventilation syndrome in the MR. This patient was excluded from the analysis. The remaining 5 patients [all male, age 24 years (20-32)] underwent the entire protocol. Patient characteristics for each patient are listed in **Table 1**.

Baseline and bicycle stress echocardiography

Baseline echocardiographic parameters are listed in **Table 1**. The RV was dilated and low normal indexes of right ventricular function at rest were found.

Patients performed submaximal on bicycle stress echocardiography with peak HR 140 bpm (range 120-142) and peak cardiac output 12 L/min (range 7.4-21). The median of peak instantaneous pressure gradient across the pulmonary homograft increased from 46 mmHg (range 12-55 mmHg) to 68 mmHg (range 43-108 mmHg) at peak exercise. **(Table 2)**

Dobutamine-stress cardiac magnetic resonance imaging

Results from volumetric measurements of the right ventricle can be found in **Table 3** and **Figure 1**. Volumetry of the left ventricle can be found in **Figure 1**.

Aortic and pulmonary valve regurgitant volume and fraction can be found in **Table 4**. No more than mild regurgitation was observed at baseline.

RV end-diastolic volumes increased in all patients from rest across the 2 stages of dobutamine infusion [from 194 ml at baseline (159-237) to 232 ml (165-255)]. RV end-systolic volumes decreased in all but 1 patient (patient 5) [from 97 ml (70-131) to 88 ml (52-117)]. In patient 5, a bimodal response with an initial decrease in end-systolic volume (from 126-117 ml), followed by an increase at 20 µg/kg/min infusion (from 117 ml to 123 ml) could be observed. RV stroke volume was decreased at 20µg/kg/min in patient 5 whereas in the other 4 patients an increase of stroke volume could be seen. **(Table 3 and Figure 1)**

When evaluating TV regurgitant volume and fraction, no increase in regurgitant volume and fraction could be seen in patients with preserved contractile reserve,

whereas in the 1 patient presenting with decreased contractile reserve, an increase of regurgitant volume and (fraction) could be seen from 4 ml (6%) at baseline to 28 ml (41%) and 23ml (34%) at 10µg/kg/ml and 20µg/kg/ml dobutamine infusion respectively.

Table 1 Demography and baseline echocardiography

Gender	n male (%)		5 (100%)
Age	Median (range)	years	24 (20-32)
BMI	Median (range)	kg/m2	22.4 (18.5-25.3)
LVEF	Median (range)	%	53 (50-56)
E' velocity	Median (range)	cm/sec	10 (8-12)
E/e'	Median (range)		7.6 (5.2-8.6)
Eccentricity index	Median (range)		1.2 (1.0-1.3)
RVFAC	Median (range)	%	0.33 (0.27-0.45)
TAPSE	Median (range)	mm	16 (15-18)
RV diameter	Median (range)	mm	36 (33-44)
RA long axis diameter	Median (range)	mm	50 (46-59)

BMI=body mass index; LVEF=left ventricular ejection fraction; RV=right ventricle; FAC=fractional area change; RA=right atrium

Table 2 Patient characteristics for cardiac output and right ventricular outflow tract gradient as assessed by echocardiography at baseline and at peak exercise. (HR=heart rate; PIP=peak instantaneous pressure; RVOT=Right Ventricular Outflow Tract)

			Baseline			**Peak exercise**		
	Gender	Age (years)	HR (bpm)	Cardiac Output (L/min)	PIP RVOT gradient (mmHg)	HR (bpm)	Cardiac Output (L/min)	PIP RVOT gradient (mmHg)
pt1	M	21	60	3.2	12	120	7.4	43
pt2	M	32	61	5.2	30	141	15	68
pt3	M	24	71	6.7	46	142	12.2	57
pt4	M	20	57	6.1	55	133	21	108
pt5	M	24	77	6.4	55	140	11.4	92

Table 3 Volumetry obtained by CMR and calculation of regurgitant volume and regurgitant fraction.

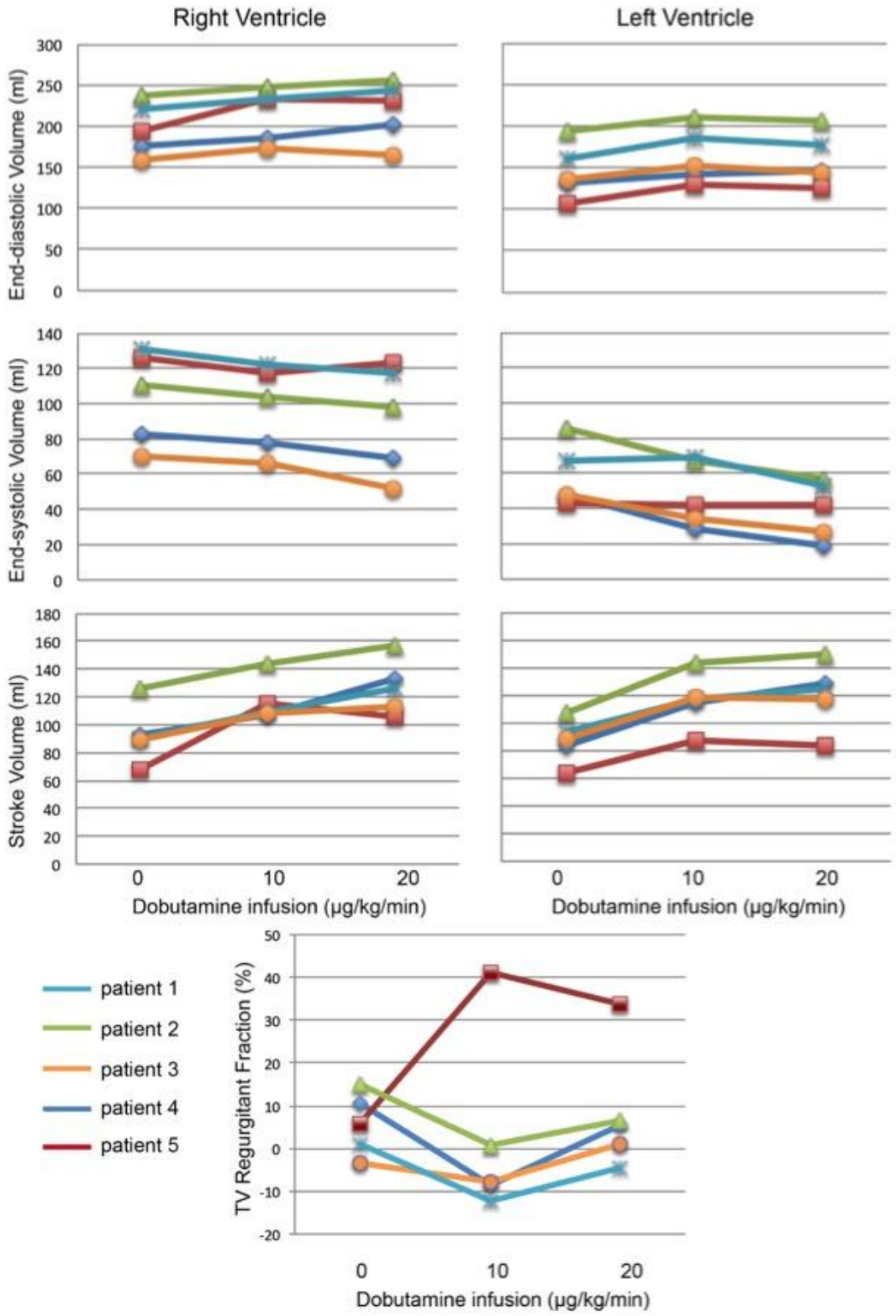
	Dobutamine (µg/kg/min)	RV EDV (ml)	RV ESV (ml)	RV SV (ml)	TV Reg Volume (ml)	TV Reg fraction
pt1	0	220	131	90	-3	-3%
	10	232	122	110	-7	-8%
	20	243	117	126	1	1%
pt2	0	237	111	126	19	15%
	10	248	104	144	1	1%
	20	255	98	157	8	6%
pt3	0	159	70	89	1	1%
	10	174	66	108	-11	-12%
	20	165	52	113	-4	-5%
pt 4	0	176	83	93	10	11%
	10	186	78	107	-8	-9%
	20	202	69	133	5	5%
pt 5	0	194	126	68	4	6%
	10	233	117	115	28	41%
	20	230	123	106	23	34%

RV: right ventricle; EDV: end-diastolic volume; ESV: end-systolic volume; SV: stroke volume; TV: tricuspid valve

Table 4 Pulmonary (PR) and aortic valve regurgitation (AR) at baseline obtained by flow velocity mapping.

	AR (ml)	AR fraction	PR (ml)	PR fraction
pt 1	1	2%	0.3	0.4%
pt 2	14	14%	14	10%
pt 3	6	8%	2	2%
pt 4	4	6%	17	17%
pt 5	5	7%	8	8%

Figure 2 Right ventricular (RV) volumes as obtained by cardiac magnetic resonance imaging. The regurgitant fraction was calculated from the difference between right ventricular stroke volume and left ventricular stroke volume derived from volumetric measurements.



Discussion

In this pilot study, we showed that decreased RV contractile reserve in patients with repaired tetralogy of Fallot might contribute to an increase in tricuspid regurgitant flow and fraction.

TR occurs from a variety of reasons and in various cardiac diseases. Right ventricular hypertension, is associated with increasing TR severity. Furthermore, increased RV pressure load leads to a more pronounced septal shift towards the left ventricle during systole. The septal chordal attachments of the tricuspid leaflets are of the utmost importance in preservation of the valvular competence and increased septal shift leads to increased leaflet tethering and tricuspid regurgitation.[13, 14]

During exercise, increased flow causes an increase in pressure gradient across the RV outflow tract. However, we have already shown that an acute increase in pressure-load during exercise doesn't result in an increase in tricuspid regurgitant severity in patients with native pulmonary valve stenosis. **(cfr. Chapter 3, paragraph 2)** These patients were all able to increase their stroke volume normally, as evidenced by an oxygen-pulse/workload relationship not different from that of healthy controls. In patients with preserved RV function, tricuspid valve competence during exercise might be preserved through smaller end-systolic volumes resulting in better approximation of the papillary muscles and less leaflet tethering. Furthermore, end-systolic volumes are decreased during exercise, and this is most likely associated with a decrease in annular circumference and hence valvular competence.[15, 16]

Dobutamine infusion has a positive inotropic and chronotropic effect as a result of stimulation of the adrenoceptors. This results in an increase in stroke volume, heart rate and cardiac output. Administration of dobutamine has been used to evaluate contractile reserve of the left ventricle, especially in the setting of low-flow/low-gradient aortic valve stenosis.[17, 18] More recently, it was used to evaluate right ventricular contractile reserve in patients with repaired tetralogy of Fallot.[10] In this study, we used both physical exercise and dobutamine stress to evaluate right ventricular hemodynamics. However, it should be noted that physical exercise and pharmacological stress have different hemodynamic effects. Contrary to physical exercise, dobutamine stress causes a decline in systemic arterial pressure and is not associated with increased venous return provided by the muscle pump. The lower left

ventricular afterload during stress results in an elevated transseptal pressure gradient during systole and can exaggerate the leftward septal shift in the setting of right ventricular outflow tract obstruction. This might lead to higher end-systolic volumes then would have been observed when left ventricular afterload was increased during exercise. Furthermore, the lower venous return during dobutamine stress might cause diminished right ventricular function due to leftward shift on the starling curve.

This setting offers the possibility to evaluate the effect of impaired contractile reserve on TR severity without the added effect of augmented preload due to increased venous return during exercise.

Our patients showed an increase in RV outflow tract gradient during bicycle stress echocardiography, although exercise was submaximal.

To evaluate RV contractile reserve, we performed dobutamine-stress CMR. An increase in RV end-diastolic volumes and a decrease in end-systolic volume were seen in 4/5 patients. The increase in RV end-diastolic volume with increasing doses of dobutamine infusion was in contrast with Parish et al, who observed a decrease in both diastolic and systolic volumes.[10] Some differences between the studied patients should be noted. Our study sample focussed on patients with a predominant RV pressure-load in contrast to the severe pulmonary regurgitation in the aforementioned study. Furthermore, interventricular dyssynchrony is often observed in patients with repaired tetralogy of Fallot and might be more pronounced during dobutamine stress.[12] As we analysed RV and LV volumes separately, this resulted in maximal end-diastolic volumes. Mechanical dyssynchrony might cause increased maximal LV and RV diastolic volumes due to septal shift, occurring at different time-points.

In 1 patient, impaired RV contractile reserve was identified. When evaluating tricuspid regurgitant fraction in this patient, we found an increase in regurgitant fraction, as evaluated by comparing left and right ventricular stroke volume. In the 4 patients with preserved contractile reserve, this increase of regurgitation severity was not seen. This patient also presented with a high pulmonary homograft gradient at rest and at peak exercise. However, patient 4 had similar characteristics and didn't present with a similar evolution in regurgitant fraction.

These findings indicate a possible relationship between right ventricular function and tricuspid regurgitant severity, although no conclusive statements can be made based on this small patient sample.

Conclusion

We observed an increase in tricuspid regurgitant fraction in 1 patient presenting with impaired right ventricular contractile reserve. Although we can't make solid conclusions given the low patient number, these findings hint towards a possible contribution of right ventricular dysfunction in preservation of tricuspid valvular competence

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Chapter 4

Onset of tricuspid regurgitation determines prognosis in pre-capillary pulmonary hypertension

Abstract

Objective

Patients with pulmonary hypertension (PH) often present with tricuspid valve regurgitation (TR). We aimed (1) to establish the impact of increasing TR severity in incident cases of patients with pre-capillary PH, (2) to evaluate the effect of new severe TR on outcome and (3) to evaluate the link between right ventricular function and TR in patients with pre-capillary PH.

Methods and results

Incident cases of patients with pre-capillary PH were included from the institutional database of PH between January 2000 and December 2012. In the diagnostic work-up, 429 patients (61% female; 60±10 years old) were diagnosed and had a transthoracic echocardiography within 3 months from the catheterisation. 193 (45%) of patients had Group 1, 28 (6.5%) Group 3, 188 (43.8%) Group 4 and 17 (4.0%) Group 5 PH according to the Dana Point classification. Follow-up was ended July 2013.

Demographic, echocardiographic and invasive catheterisation data at inclusion were analysed. Primary endpoint was all-cause mortality. Median follow-up time was 10.7 years. During follow-up, 159 patients died. Five-year survival of the entire cohort was 66%.

Multivariate cox regression, including baseline parameters age, gender, tricuspid annular plane systolic excursion (TAPSE) (18±5 mm), indexed right atrial long-axis diameter (30±5 mm), indexed right ventricular diameter (25±5 mm), pulmonary vascular resistance (9.7±5.2 Wood Units) and TR severity (2.5±0.9/4) revealed *age* [HR 1.029 (1.012-1.047); p=0.001] and *TR* [HR 1.579 (1.206-2.067); p=0.001) as independently associated with mortality. When development of severe TR>2/4 was modelled as a time dependent covariate, *age* [HR 1.031 (1.015-1.048); p=0.001], *development of severe TR* [HR 2.323 (1.398-3.862); p=0.001] and *TAPSE at inclusion* [HR 0.946 (0.903-0.990); p=0.017] emerged as predictors of outcome.

From the 204 (48%) patients presenting with TR ≤ 2/4, 50 patients developed TR > 2/4 during follow-up. From the consecutive echocardiographic measurements of tricuspid annular plane systolic excursion (TAPSE) and the ratio TAPSE/pulmonary artery systolic pressure (PASP) before the onset of TR, a linear regression slope was

calculated for each individual patient. Decrease in TAPSE (1mm per year; HR 1.052 (1.013-1.092); p=0.009) or TAPSE/PASP ratio (0.1 mm/mmHg per year; HR 1.168 (1.075-1.268); p<0.001) was predictive for the onset of TR>2/4.

Conclusions

TR severity is independently related to worse outcome in patients with pre-capillary PH. Furthermore, survival is impaired if patients develop significant TR during follow-up. Severe TR is preceded by a progressive decline of right ventricular function.

Introduction

Pulmonary hypertension (PH) occurs in a variety of diseases and is associated with impaired prognosis.[1, 2] It is defined as a mean pulmonary artery pressure ≥ 25 mmHg on right heart catheterisation. Currently, patients with PH are classified according to the DANA point classification into 5 groups.[1] The majority of patients have PH due to left-heart disease (Group 2), so-called post-capillary PH, characterized by high left atrial pressures > 15 mmHg. In these patients PH is either a marker of prognosis as well as an indication for surgical intervention for instance in mitral valve surgery. On the other hand, pre-capillary PH consists of patients with pulmonary arterial hypertension (Group 1), PH due to lung disease or hypoxia (Group 3), chronic thromboembolic PH (group 4) and PH due to unclear or multifactorial mechanisms (Group 5) and originates from within the pulmonary circulation, either because of thrombus formation or due to vascular remodelling.[3] In these patients, even with modern targeted therapy, outcome is impaired also if they respond to therapy.[4] Therefore, there is a continuing search for means to improve prognosis.

Tricuspid regurgitation (TR) is often observed in patients with pre-capillary PH.[5] It originates from increased pulmonary pressure, right ventricular dilatation and remodelling, and tricuspid annular dilation.[6] In many diseases, the presence of TR is independently associated with worse prognosis.[7] However, the impact of TR on outcome in patients with pre-capillary pulmonary hypertension is not fully understood. Even more so, TR is often encountered in the presence of right

ventricular dysfunction. Nonetheless, it is unclear whether TR is a symptom rather than a disease, eventually causing the right ventricle to fail.

Determination of right ventricular function is difficult, especially in the pressure-loaded ventricle. Indices of right ventricular function are load dependent. Therefore, interpretation of the results obtained should be performed in conjunction with the force developed, i.e. systolic pulmonary artery pressure. Guazzi et al. proposed an easy, non-invasive parameter to evaluate the length-force relationship of the right ventricular myocardium by dividing tricuspid annular plane systolic excursion (TAPSE) by Doppler derived pulmonary artery systolic pressure (PASP).[8]

Therefore, we aimed (1) to establish the impact of increasing TR severity in incident cases of patients with pre-capillary PH, (2) to evaluate the effect of new severe TR on outcome and (3) to evaluate the link between right ventricular function and TR in patients with pre-capillary PH.

Methods

Patient selection and data collection

From the specialised institutional database of PH, patients undergoing right heart catheterization as part of the diagnostic work-up for PH were included between January 2000 and December 2012.

Incident cases of patients with pre-capillary PH, diagnosed as a mean PAP $\geq$ 25 mmHg and pulmonary capillary wedge (PCW) < 15 mmHg were included. Diagnostic work-up was completed according to present guidelines and patients were classified into groups of PH according to the DANA point classification.

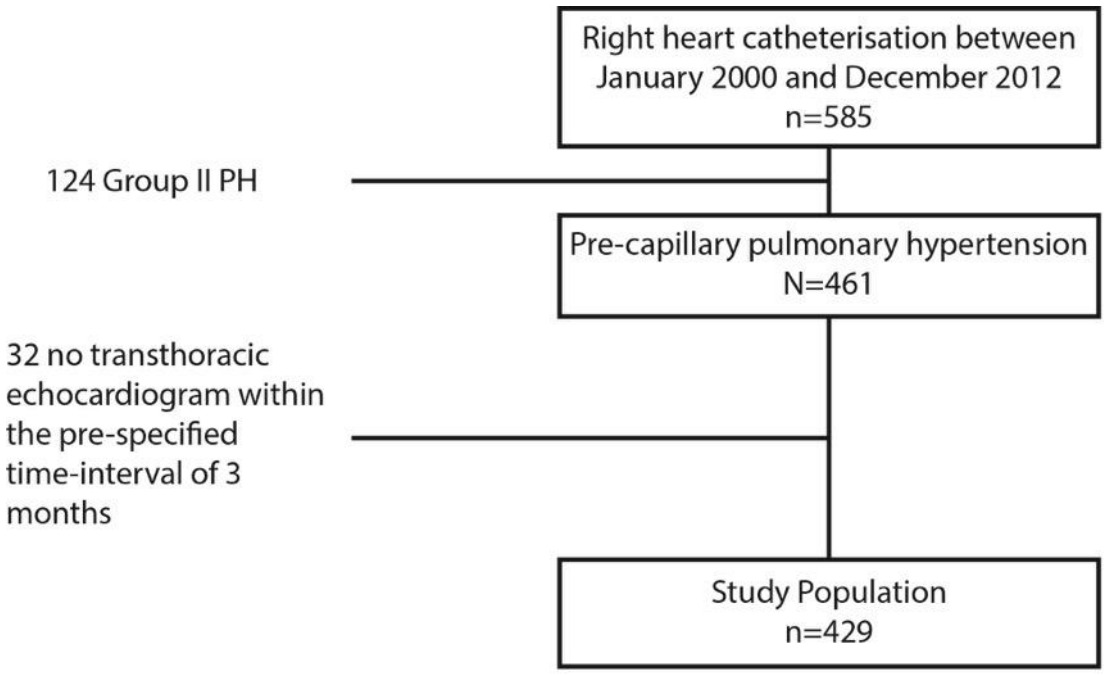
Of 585 patients undergoing right heart catheterisation, 124 patients were diagnosed with PH due to left-sided heart disease (Dana point Group 2), 32 didn't have a transthoracic echocardiogram within 3 months from the right heart catheterisation. This resulted in a total of 429 patients eligible for analysis.

The ethics committee approved patient inclusion and data analysis.

Right heart catheterisation

A Swan-Ganz catheter was inserted under local anaesthesia from the internal jugular or the femoral vein and placed at the level of the right heart. Invasive measurement of mean right atrial pressure; systolic, diastolic and mean pulmonary artery pressure and pulmonary capillary wedge pressure was obtained. Cardiac output was evaluated by the thermodilution method. Pulmonary vascular resistance in Wood Units was calculated as (meanPAP-PCW)/Cardiac output. The date of catheterisation was taken as the inclusion date.

Figure 1 Inclusion algorithm.



Transthoracic echocardiography at baseline and during follow-up

Standard transthoracic echocardiography was performed in all subjects at baseline within a pre-specified timeframe of 3 months. Furthermore, echocardiographic measurements during follow-up were included as well. Development of severe TR was defined as TR>2/4 on 2 consecutive visits. Measurement of the right atrium was done from an apical 4-chamber view measuring the long axis at end-systole. The right ventricular diameter was measured from an apical 4-chamber view at the mid-ventricular level at end-diastole. Right atrium and right ventricular diameter were

indexed for body surface area, calculated with the Mosteller formula. Tricuspid annular plane systolic excursion (TAPSE) was measured from an M-mode placed through the tricuspid annulus from an apical 4-chamber view. The tricuspid regurgitant gradient (TRG) was obtained by continuous wave Doppler examination of the tricuspid valve regurgitant jet during systole. Pulmonary artery systolic pressure (PASP) was calculated from the TRG by the simplified Bernoulli equation and an estimate of right atrial pressure was added. Right atrial pressure was estimated from the diameter and respiratory variation of the inferior vena cava (IVC). It was assumed 5 mmHg if IVC diameter was < 2 cm and respiratory variation was > 50%, 10 mmHg if IVC<2 cm and respiratory variation < 50%, and 15 mmHg if IVC expiratory diameter was > 2 cm. From the obtained measurements, the ratio of TAPSE/PASP was calculated at each time point during follow-up.[9]

Other standard measurements were done according to the guidelines of echocardiography.[10]

Statistical analysis:

Continuous data and categorical data are represented by means and standard deviation or frequencies and percentages respectively.

First, demographic data, invasive catheterisation and echocardiographic data at inclusion were analysed. Kaplan-Meier survival analysis was performed to evaluate all-cause mortality in the total cohort of patients. The primary endpoint for the survival analysis was all-cause mortality.

Second, univariate and multivariate cox regression was performed to identify factors associated with outcome.

Third, development of severe TR > 2/4 was modelled as a time-dependent covariate and multivariable cox regression with the same parameters was performed.

Fourth, the evolution of TAPSE and TAPSE/PASP ratio was evaluated in patients presenting without severe TR (≤2/4) at inclusion. For each patient, linear regression of the studied parameter as a function of the time from inclusion until development of severe TR was performed. The unstandardized β-coefficient was used as the slope of TAPSE, TAPSE/PASP respectively to represent the evolution of right ventricular function before onset of severe TR. The number of observation for each patient was

used to perform a weighted analysis. Univariate cox regression with each slope weighted and normalized for the number of observations was used to evaluate the association of right ventricular deterioration with the occurrence of severe TR (>2/4).

All tests were two-tailed. A P-value <0.05 was considered significant. Analyses were performed using SPSS® (version 20) and SAS®.

Results

Patient inclusion:

Data from eligible patients were available for 429 patients, 61% female, aged 60 yrs. ± 15. Pulmonary arterial hypertension (Group 1) was diagnosed in 193 (45%) patients, PH due to lung disease (Group 3) in 28 (6.5%), chronic thromboembolic pulmonary hypertension (Group 4) in 188 (43.8%) and PH from unknown or multifactorial mechanism (Group 5) in 17 (4.0%) patients. [11] **(Figure 2)** From 429 patients included, 225 had TR > 2/4 at inclusion. From the 204 patients presenting with TR ≤ 2/4, 50 patients developed TR > 2/4 during follow-up.

During a median follow-up time of 10.7 years, 159 patients died. Five-year survival of the entire cohort was 66%.

Baseline determinants of outcome:

Univariate analysis showed age (HR 1.033 (1.02-1.046); p<0.0001); TR severity (HR 1.765 (1.45-2.149); p<0.0001); RA index (HR 1.065 (1.036-1.094); p<0.0001); RV index (HR 1.042 (1.01-1.075); p=0.01); Right atrial pressure (HR 1.05 (1.021-1.08); p=0.001) and TAPSE (HR 0.938 (0.901-0.976); p=0.002) associated with all-cause mortality. On multivariate cox regression, only age (HR 1.56 (1.189-2.047); p=0.001) and TR severity (HR 1.031 (1.013-1.048); p=0.001) emerged as independent predictors of outcome.

Evaluation of progression of TR on outcome

Multivariate cox regression, showed that patients that developed TR > 2/4 during follow-up had a 2 fold increase in the hazard of dying (HR 2.296 (1.379-3.822); p=0.001). **(Table 3)** Furthermore, both older age (HR 1.032 (1.016-1.049); p=0.001)

and lower TAPSE at baseline (HR 0.949 (0.906-0.994); p:0.026) emerged as independent predictors of all-cause mortality.

Evaluation of right ventricular function in the occurrence of severe TR in follow-up

We could observe a strong relation between the evolution of TAPSE and TAPSE relative to PASP in the pathogenesis of severe TR. **(Table 4)** For each decrease of 1mm/year in TAPSE, this is associated with a 5% increase in hazard to develop TR>2/4. Similarly, for decrease of 0.1 units (mm/mmHg) of the TAPSE/PASP ratio per year, this corresponds with a 17% increase in hazard of the occurrence of TR>2/4.

The development of TR is represented graphically in **Figure 3**, for 2 groups split by the median of the slope of the TAPSE-time relationship and (B) for each quartile of the slope of the TAPSE/PASP-time relationship.

Figure 2 Composition of the studied population (n=429). Categories are based on the current Dana point classification for pulmonary hypertension.

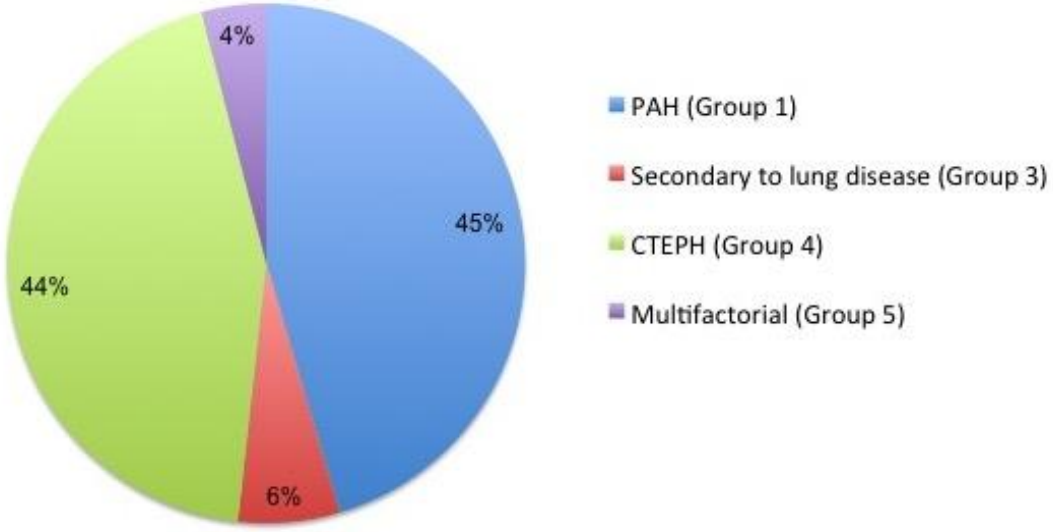


Table 1 Demography, data from right heart catheterisation and from transthoracic echocardiography at baseline.

		N	Total study sample
Demography			
Age (years)	mean±SD	429	60 ± 15
Female gender	n (%)	429	263 (61%)
BSA (m^2)	mean±SD	383	1.9 ± 0.2
Right heart catheterisation			
RAP (mmHg)	mean±SD	422	8 ± 5
sysPAP (mmHg)	mean±SD	421	76 ± 20
diasPAP (mmHg)	mean±SD	421	29 ± 10
meanPAP (mmHg)	mean±SD	429	45 ± 12
PCW (mmHg)	mean±SD	426	9 ± 4
PVR (Wood Units)	mean±SD	423	10 ± 5
Cardiac Output (L/min)	mean±SD	423	4.2 ± 1.3
Cardiac Index (L/min/kg	mean±SD	413	2.3 ± 0.6
Echocardiography			
LVEF (%)	mean±SD	382	65 ± 9
LVEDD (mm)	mean±SD	380	41 ± 7
RA diameter (mm)	mean±SD	414	55 ± 8.5
RA index (mm/m^2)	mean±SD	374	30 ± 5
RV diameter (mm)	mean±SD	416	46 ± 9
RV index (mm/m^2)	mean±SD	376	25 ± 5
TAPSE (mm)	mean±SD	369	18 ± 5
TAPSE/PASP (mm/mmHg)	mean±SD	358	0.26±0.15
TR 0/4	n (%)		4 (1%)
1/4	n (%)		56 (13%)
2/4	n (%)		136 (32%)
3/4	n (%)		161 (38%)
4/4	n (%)		64 (15%)
TR regurgitant gradient (mmHg)	mean±SD	416	69 ± 20

Table 2 Univariable and multivariable (n=327) cox regression for baseline demographic, echocardiographic and invasive parameters.

	Univariable			Multivariable		
	N	**HR (95% CI)**	**P-value**	**N**	**HR (95% CI)**	**P-value**
Age (years)	429	1.033 (1.02-1.046)	p<0.0001*	327	1.031 (1.013-1.048)	0.001*
TR (x/4)	421	1.765 (1.45-2.149)	p<0.0001*		1.56 (1.189-2.047)	0.001*
PVR (Wood Units)	423	1.014 (0.982-1.046)	0.399		0.992 (0.945-1.041)	0.74
RAP (mmHg)	422	1.05 (1.021-1.08)	0.001*		1.02 (0.981-1.06)	0.314
RV index (mm/m2)	376	1.042 (1.01-1.075)	0.01*		0.998 (0.947-1.051)	0.931
RA index (mm/m2)	374	1.065 (1.036-1.094)	<0.0001*		1023 (0.969-1.079)	0.415
TAPSE (baseline) (mm)	369	0.938 (0.901-0.976)	0.002*		0.964 (0.917-1.014)	0.158
Gender	429	1.089 (0.772-1.538)	0.627		1.247 (0.818-1.899)	0.305
MeanPAP (mmHg)	429	1.006 (0.992-1.019)	0.42			
LVEF (%)	382	0.991 (0.973-1.01)	0.366			

TR=tricuspid regurgitation; TAPSE=tricuspid annular plane systolic excursion; RA=right atrium; RV=right ventricle; RAP=right atrial pressure; PVR=pulmonary vascular resistance; meanPAP=mean pulmonary artery pressure. *P<0.05=significant.

Table 3 Multivariable cox regression with evolution towards severe TR as time-dependent covariate. Progression of TR was defined as TR>2/4 on 2 consecutive outpatient or hospital visits.

	N	**HR (95% CI)**	**P-value**
Progression of TR	327	2.296 (1.379-3.822)	0.001*
Age (years)		1.032 (1.016-1.049)	<0.0001*
Gender		1.272 (0.868-1.865)	0.217
TAPSE (baseline) (mm)		0.949 (0.906-0.994)	0.026*
RA index (mm/m^2)		1.021 (0.973-1.072)	0.396
RV index (mm/m^2)		0.996 (0.948-1.045)	0.865
RAP (mmHg)		1.018 (0.983-1.055)	0.326
PVR (Wood units)		0.976 (0.932-1.023)	0.312

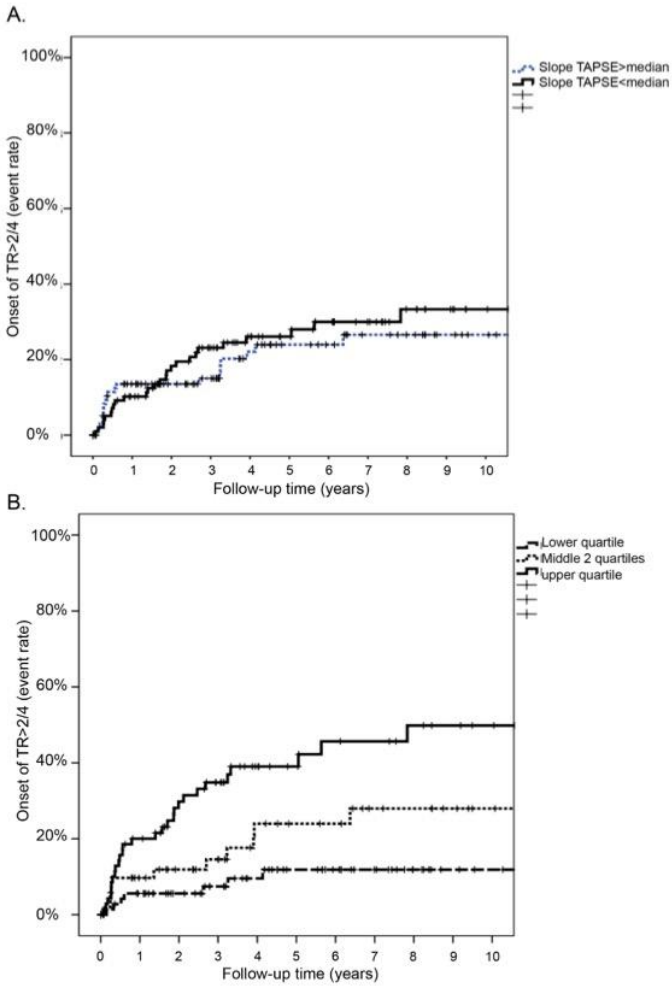
TAPSE=tricuspid annular plane systolic excursion; RA=right atrium; RV=right ventricle; RAP=right atrial pressure; PVR=pulmonary vascular resistance. *P<0.05=significant.

Table 4 Cox regression with onset of TR as outcome, implementing evolution of TAPSE (1 mm per year) or TAPSE relative to PASP (0.1 mm/mmHg per year) as covariate.

	N	HR (95% CI)	P-value
Slope of TAPSE	197	1.052 (1.013-1.092)	0.0092*
Slope of TAPSE/PASP	196	1.168 (1.075-1.268)	0.0002*

TAPSE=tricuspid annular plane systolic excursion; PASP=pulmonary artery systolic pressure. P<0.05=significant.

Figure 3 Cumulative incidence ratio for the development of TR > 2/4 for (A) the slope of the TAPSE-time relationship split by median slope (=0) and (B) the slope of the TAPSE/PASP-time relationship for each quartile (Quartile 1 < -0.009361; Quartile 2&3 = -0.009361-0.012763; Quartile 4 > 0.012763).



Discussion

This study shows that TR severity at baseline has an impact on prognosis in patients with pre-capillary PH. Moreover, the development of severe TR impairs prognosis. Furthermore, in patients with pre-capillary pulmonary hypertension, a decrease in RV function over time is associated with TR progression.

The effect of TR on prognosis has long been debated. Although TR is known to impact prognosis, it is still unclear if TR is the cause, or merely an indicator of worse survival.[7] When performing cross-sectional studies, an inverse relation between right ventricular function and TR severity can be seen.[12] However, based on these results it is difficult to determine a causative relation. Our study shows that TR at inclusion is an independent predictor of outcome in patients with pre-capillary PH. Furthermore; the development of TR is associated with worse outcome independently of baseline parameters. This suggests a causative relationship, with the added volume-load on the already pressure-loaded ventricle leading to accelerated right ventricular dysfunction.

Although TR is reasonably well tolerated for a long period in the normal RV, eventually ventricular failure ensues and heart symptoms of heart failure develop.[13] The volume-load associated with TR increases stroke work of the RV. However, the RV, with its thin walled and compliant ventricle, seems to be well adjusted to support this volume load for a long time.[14, 15] On the other hand, a pressure-load is associated with early remodelling of the right ventricle, with a thicker and less compliant ventricular wall and a more spherical geometry.[14] Moreover, the stroke work further increases when a combination of pressure- and volume load is present.

Studies in patients with congenitally corrected transposition of the great arteries have shown rapid deterioration of the right ventricular function at the moment TR develops.[16, 17] In these patients, RV dysfunction is seldom encountered without severe TR. Furthermore, in these patients maintenance of tricuspid valvular competence is associated with better prognosis and if TR occurs, surgery before RV ejection fraction is <44% seems to stop the onset of RV dysfunction.

If this is also applicable to patients with pre-capillary PH is not clear. If so, RV function should be preserved at the time of development of TR. In contrast with this, we found that deterioration of RV function is predictive for the development of severe TR. Especially the TAPSE/PASP ratio, a representation of the length/force

relationship of the right ventricle is a strong predictor of severe TR. [9] In the assessment of right ventricular function in pre-capillary PH, obtained values are often difficult to interpret. Indeed, many parameters of right ventricular function are load-dependent, especially if pulmonary vascular resistance is raised and right ventricular afterload is consequently increased.[18] The use of TAPSE relative to PASP provides an index of the right ventricular force-length relationship as it relates the longitudinal shortening of the muscle fibers to the force developed.[8]

Interpreting these results, it seems TR is a symptom of progressive right ventricular deterioration. However, the development of severe TR is a strong predictor of outcome in this patient population. It seems that progressive RV dysfunction eventually leads towards more severe TR and this added volume-load causes a vicious circle of added volume-load, further deterioration of RV function and eventually death. To stop rapid deterioration of right ventricular function, it is tempting to suggest surgical correction of TR. However, in the setting of pre-capillary PH, progressive right ventricular dysfunction due to persistent pressure-load will probably ensue after surgery. Indeed, we showed that the presence of PH is associated with worse survival when isolated tricuspid valve surgery is performed.[19] Conversely, in the setting of functional TR, secondary to left-sided heart disease, studies show favourable remodelling and clinical benefit of tricuspid annuloplasty in combination with mitral valve surgery. In these patients, correction of the left-sided valvular disease lowers pulmonary arterial pressures. In these patients, there seems to be an additional benefit of removal of the volume-load associated with TR to preserve right ventricular function for a longer time. (Chapter 5, section 2)

The development of severe TR indicates therefore worse prognosis and should trigger close follow-up and/or might be an indication for dose adjustment of targeted therapy. Even more so, TAPSE and TAPSE/PASP relationship should be monitored during follow-up, with a decrease indicative for disease progression.

However, prospective studies are needed to prove the additional benefit of early dose adjustment of specific vasodilator therapy in the case of progression TR and decline in TAPSE or TAPSE/PASP ratio.

Conclusion

Tricuspid regurgitation and the development of severe TR during follow-up are associated with increased mortality. Right ventricular function deterioration is predictive for the development of TR. If TR severity increases and if indices of right ventricular function deteriorate over time, the treatment of the patient should be re-evaluated.

Limitations

Our results are based on a retrospective analysis of patients followed in a single institution. The patients in this study cohort were classified according to the Dana point classification of 2008, in use at the time of study design and conduct.[11] However, a new classification, Nice 2013, has been recently introduced.[20]

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Chapter 5

Management of tricuspid regurgitation

1 Outcome and determinants of prognosis in patients undergoing isolated tricuspid valve surgery: Retrospective single centre analysis.

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Published in *International Journal of Cardiology, August 2014*

2 Additional tricuspid annuloplasty in mitral valve surgery results in better clinical outcome: a propensity matched analysis.

De Meester P, De Cock D, Van De Bruaene A, Gabriels C, Buys R, Helsen F, Voigt J-U, Herijgers P, Herregods M-C, Budts W.

Manuscript under revision, *Heart*

1. Outcome and determinants of prognosis in patients undergoing isolated tricuspid valve surgery: retrospective single centre analysis.

Abstract

Aims

Although tricuspid valve (TV) surgery has become more popular, isolated TV surgery is infrequently performed. The aims of this study were (1) to evaluate the postoperative and long-term mortality of patients undergoing isolated TV surgery, (2) to compare the outcomes of patients undergoing their first TV surgery or TV reoperation, and (3) to assess the additive value of echocardiographic and invasive hemodynamic evaluations for predicting postoperative outcome.

Methods

We followed a contemporary cohort of patients undergoing isolated TV surgery from January 1, 1995, through December 31, 2011. Preoperative demographic, echocardiographic, hemodynamic, and operative data were included. Outcome was all-cause mortality.

Results

Ninety-two patients (38% male; mean age: 56±14 years) were included. Kaplan-Meier survival analyses showed that 30-day, 3-month, 5-year, and 10-year mortality were 7.9%, 15.2%, 25.7%, and 53.7%, respectively. No difference in outcome was found between patients undergoing first TV surgery (n=61) and TV reoperation (n=31) (p=0.669). Univariable Cox analysis identified age (p<0.0001), extracardiac vascular disease (p=0.001), glomerular filtration rate (p=0.022), NYHA classification (p=0.010), and mean pulmonary artery pressure (p=0.005) as predictors of mortality. Multivariable analysis identified significant associations with outcome, only for age (p=0.010) and NYHA functional class (p=0.044). In younger patients (<59 years), mean pulmonary artery pressure was associated with the worse outcome (p=0.024).

Conclusions

Isolated TV surgery is still associated with important postoperative and long-term mortality, both for first TV surgery and TV reoperation. Pre-operative NYHA functional class and, in younger patients, pulmonary hypertension appear to determine prognosis.

Introduction

In recent years, interventions involving the tricuspid valve (TV) have become increasingly popular. European Society of Cardiology guidelines have recently been updated and now advocate a more liberal approach towards TV surgery, especially in combination with operations on left-sided valves.[1] On the other hand, AHA/ACC guidelines are largely silent on tricuspid valve surgery.[2] However, a registry describing hospital admissions for TV surgery in the United States showed that the number of tricuspid procedures more than doubled from 1999 to 2008.[3]

TV disease affects morbidity and mortality as well as functional capacity in different types of heart disease.[4-10] The great majority of TV interventions is performed due to tricuspid regurgitation, most often secondary to left-sided valvular disease. Although a low threshold to perform TV surgery in conjunction with mitral valve surgery is currently advocated, isolated TV surgery is still infrequently performed.[3] ESC guidelines advise isolated TV intervention if patients are symptomatic and tricuspid regurgitation is severe. TV surgery can be considered if tricuspid regurgitation is severe and signs of right ventricular dilatation or dysfunction are present.[1] However, if tricuspid regurgitation is severe and surgery is postponed, right ventricular failure can develop, increasing morbidity and mortality dramatically.[11, 12]

Determining when to perform isolated TV surgery remains difficult. Registries and small studies have shown that isolated TV surgery is still associated with significant perioperative morbidity and mortality, especially when compared to left-sided valve surgery.[13-17] However, studies on the postoperative and long-term outcomes of isolated TV surgery are scarce and often include patient cohorts operated decades ago, making application to present-day patient care difficult.

Therefore, the aims of the present study were (1) to evaluate the postoperative and long-term mortality of patients undergoing isolated TV surgery, (2) to compare the outcomes of patients undergoing first TV surgery or TV reoperation, and (3) to assess the additive value of pre-operative echocardiographic and invasive hemodynamic evaluations for predicting outcome after surgery.

Methods

Population and Data Collection

We followed a contemporary cohort of consecutive patients undergoing isolated TV surgery at the University Hospitals Leuven in Leuven, Belgium between January 1, 1995, and December 31, 2011. Data were collected at the time of surgery and stored in the database of cardiac surgery. A search from the database of cardiac surgery was performed and data were exported for analysis after review of each patient file for completeness of the data studied. Follow-up of patients for all-cause mortality ended January 1, 2012. Echocardiography and invasive hemodynamic assessment via cardiac catheterization were performed within 2 months before surgery. Patients had to be older than 18 years of age at the time of surgery to be included in our study. All patients underwent isolated TV surgery (first TV surgery or TV reoperation), during which the TV was repaired or replaced with a biological or mechanical prosthesis.

The local ethics committee approved the selection process and the review of the data.

Variables

Preoperative demographic, echocardiographic and hemodynamic data as well as operative data were included in the analysis. Thirty-day, 3-month postoperative, and long-term follow-up of all-cause mortality were considered as outcomes.

Preoperative demographic variables included age; gender; body mass index; cardiac risk profile (including currently smoking, presence of diabetes mellitus, high blood pressure, hypercholesterolemia, family history of coronary artery disease); extracardiac vascular disease (carotid endarterectomy, carotid disease defined as total occlusion or >50% stenosis of the carotid arteries, clinical claudication, amputation due to peripheral vascular disease); previous cardiac surgery; recent myocardial infarction (<90 days preoperatively); angina; chronic lung disease; renal function

(glomerular filtration rate as calculated using Cockcroft-Gault formula); cardiac rhythm (sinus rhythm, atrial fibrillation, or pacemaker dependent); New York Heart Association (NYHA) functional class; cause of valvular disease (primary TV disease defined as disease of the TV leaflets and secondary annular dilatation defined as dilatation of the tricuspid annulus causing tricuspid regurgitation (TR) but with intact leaflets); urgency grade of TV surgery; and type of TV surgery (annuloplasty, valve replacement with a bioprosthetic or mechanical valve). The use of loop diuretics, potassium sparing diuretics, ACE-inhibitor or angiotensin receptor blocker and beta-blockade was included. The EuroScore II was calculated for each patient.[18]

Echocardiographic variables included the grade of TR as assessed by colour Doppler imaging, right ventricular (RV) end-diastolic diameter, right atrial (RA) end-systolic diameter, right ventricular function assessed by eyeballing, tricuspid regurgitant gradient, calculated from the CW Doppler velocity of the tricuspid regurgitant jet and left ventricular ejection fraction. The RV diameter was measured at end-diastole at the mid-ventricular level in the apical 4-chamber view. The RA long-axis dimensions were measured at end-systole in the apical 4-chamber view. [19, 20] Right ventricular function was graded by eyeballing and was graded as normal, mild, moderate or severe impairment. Furthermore, digitally available echocardiographic images were reanalysed for tricuspid annular plane systolic excursion (TAPSE).

Hemodynamic variables included right atrial pressure; systolic and diastolic right ventricular pressure; and systolic, diastolic, and mean pulmonary artery pressure (PAP), determined invasively by right heart catheterization. Postoperative, in-hospital (<3 months) complications were reoperation due to bleeding; cardiac tamponed; valve dysfunction or postoperative myocardial infarction; infection (sternal infection, sepsis); cerebrovascular accident or transient ischemic stroke; pulmonary events (pulmonary embolism or pneumonia) and the need for artificial ventilation; renal failure and the need for renal dialysis; postoperative heart block; postoperative arrhythmias; and pleural effusion.

Statistical Analysis

Data are presented as means ± standard deviations or as numbers and proportions where appropriate. Firstly, the Kaplan-Meier method was used to estimate survival probabilities in the total population. Secondly, the patient population was divided into

two groups based on prior TV surgery: one group consisted of patients undergoing their first TV surgery; another group consisted of patients undergoing TV reoperation. Baseline characteristics of both groups were compared by using unpaired t-test, Pearson's chi-square, or Fishers' exact test where appropriate. Multivariable analysis was performed to evaluate the effect of TV reoperation on post-operative survival. Thirdly, on the total population, we performed univariable and multivariable analyses using the Cox proportional hazards model to identify predictors of outcome in the total population. Kaplan Meier and log rank analysis was performed for comparison of survival in patients presenting in NYHA 1-2 compared to NYHA 3-4. Because PAP is age-dependent, we split the study-population according to median age and we checked for interactions between age and mean PAP.[21] P<0.1 was considered significant for interactions. Cox proportional hazards were recalculated for mean PAP in both age groups. Pulmonary hypertension (PH) was defined as a mean PAP ≥ 25 mmHg on right heart catheterization. Kaplan Meier analysis was performed for both age groups, followed by a log-rank test after stratification into "no PH" and "PH".

Data were analysed using SPSS® (version 20, SPSS, Chicago). All tests were two-tailed, and p<0.05 was considered significant.

Results

Population Characteristics, Postoperative Events, and Outcome Mortality

We included 92 patients (38% male; mean age: 56 ± 14 years) in the analysis. Demographic data and indication for TV operation are summarized in Tables 1 and 2, respectively. All but one of the patients underwent sternotomy as opposed to lateral thoracotomy. Detailed information regarding postoperative (in hospital and <3 months) complications is listed in **Table 3**. The 30-day in-hospital mortality for the total population was 7.9%, 3-month mortality was 15.2%, 5-year mortality was 25.7%, and 10-year mortality was 53.7% **(Figure 1)**.

Comparison of First Intervention and TV Reoperation

Sixty-one patients (66%) underwent their first TV intervention, while 31 patients (34%) underwent TV reoperation. Of the 61 patients undergoing their first intervention on the TV, 26 (42.6%) already underwent prior cardiovascular surgery by

median sternotomy. Baseline characteristics and comparison between the two groups are listed in **Tables 1 and 2**. The Euro Score II was significantly higher in patients who underwent reoperation on the TV. Patients who underwent first TV intervention had significantly more TR and had more dilated right ventricles. Significantly more TV reoperation patients experienced postoperative high-grade atrioventricular block and needed implantation of a definitive pacemaker **(Table 3)**. On multivariable analysis, including TV reoperation, previous cardiac surgery by median sternotomy, age and the EuroScore II, no significant association of TV reoperation on outcome was observed (HR 1.273 (0.420-3.860); p=0.669).

Figure 1 Kaplan-Meier curve showing the overall survival in the total population. The 30-day in-hospital mortality for the total population was 7.9%, 3-month in-hospital mortality was 15.2%, 5-year mortality was 25.7%, and 10-year mortality was 53.7%.

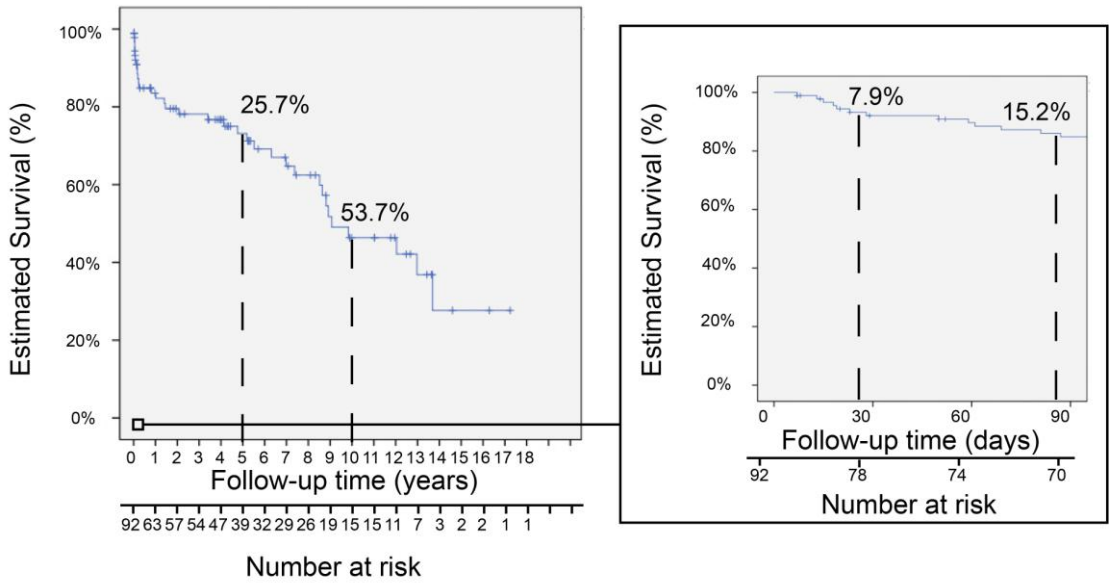


Table 1 Demographic, Echocardiographic and Hemodynamic Parameters in the Total Population and Comparison between First TV surgery and TV Reoperation.

		Total		First TV surgery		TV reoperation		P-value
Demographics								
		N		N		N		
Age (years)	(mean ± SD)	92	56 ± 14	61	58 ± 13	31	53 ± 16	0.128*
Gender	n male (%)	92	35 (38%)	61	23 (37.7%)	31	12 (38.7%)	0.925†
BMI (kg/m^2)	(mean ± SD)	91	24.6 ± 4.5	60	24.9 ± 4.6	31	23.9 ± 4.3	0.326*
Number of risk factors: 0	n (%)	88	38 (43.2%)	57	21 (36.8%)	31	17 (54.8%)	0.586‡
1			30 (34.1%)		21 (36.8%)		9 (29%)	
2			13 (14.8%)		9 (15.8%)		4 (12.9%)	
3			5 (5.7%)		4 (7%)		1 (3.2%)	
4			2 (2.3%)		2 (3.5%)		0 (0%)	
5			0 (0%)		0 (0%)		0 (0%)	
Extracardiac vascular disease	n (%)	92	5 (5.4%)	61	3 (4.9%)	31	2 (6.5%)	1‡
Previous cardiac surgery	n (%)	92	57 (62%)	61	26 (42.6%)	31	31 (100%)	<0.0001†
Recent MI (<90 days)		92	3 (3.3%)	61	3 (4.9%)	31	0 (0%)	0.548‡
Angina pectoris		92	8 (8.7%)	61	5 (8.2%)	31	3 (9.7%)	1‡
Chronic lung disease	n (%)	91	9 (9.8%)	60	7 (11.7%)	31	2 (6.5%)	0.713‡

Table 1 continued

Renal function: GFR>85 ml*min^{-1}	n (%)	92	31 (33.7%)	61	22 (36.1%)	31	9 (29.0%)	‡
GFR 50-85 ml*min^{-1}			34 (37.0%)		20 (32.8%)		14 (45.2%)	
GFR<50 ml* min^{-1}			27 (29.3%)		19 (31.1%)		8 (25.8%)	
Cardiac rhythm: sinus		92	40 (43.5%)	61	31 (50.8%)	31	9 (29%)	0.061†
AF			31 (33.7%)		20 (32.8%)		11 (35.5%)	
pacemaker			21 (22.8%)		10 (16.4%)		11 (35.5%)	

Table 1 continued

NYHA 1	n (%)	90	1 (1.1%)	59	0 (0%)	31	1 (3.2%)	0.078‡
2			24 (26.7%)		20 (33.9%)		4 (12.9%)	
3			48 (53.3%)		29 (49.2%)		19 (61.3%)	
4			17 (18.9%)		10 (16.9%)		7 (22.6%)	
EuroScoreII	%±SD	92	5.2±4.1	61	4.5±3.8	31	6.5±4.4	0.021*
Preoperative heart failure treatment								
Loop diuretics		88	53 (60.2%)	58	34 (58.6%)	30	19 (63.3%)	0.819†
Potassium sparing diuretics		88	43 (48.9%)	58	27 (46.6%)	30	16 (53.3%)	0.373†
ACE-I or ARB		88	31 (35.2%)	58	22 (37.9%)	30	9 (30.0%)	0.491†
Beta-blockade		88	37 (42.0%)	58	26 (44.8%)	30	11 (36.7%)	0.502†

Table 1 continued								
Hemodynamics (mmHg)								
RAP (mmHg)	mean ± SD	65	14.2 ± 6.0	41	13.9 ± 6.6	24	14.9 ± 5.1	0.515*
RVP_{sys} (mmHg)	mean ± SD	65	38.5 ± 13.3	41	38.4 ± 11.6	24	38.8 ± 16.0	0.923*
RVP_{diast} (mmHg)	mean ± SD	64	10.4 ± 5.7	40	10.7 ± 5.6	24	9.9 ± 6.1	0.582*
PAP_{syst} (mmHg)	mean ± SD	69	37.7 ± 13.9	46	37.6 ± 12.4	23	37.9 ± 16.8	0.947*
PAP_{diast} (mmHg)	mean ± SD	69	16.5 ± 6.4	46	16.5 ± 6.0	23	16.4 ± 7.2	0.947*
PAP_{mean} (mmHg)	mean ± SD	63	24.2 ± 9.2	40	23.8 ± 8.5	23	24.8 ± 10.6	0.667*
PH vs. no PH (mean PAP ≥ 25 mmHg)	n (%)	63	32 (50.8%)	40	19 (47.5%)	23	13 (56.5%)	0.490†
Echocardiography								
TR								
0/4	n (%)	90	1 (1.1%)	60	0 (0%)	30	1 (3.3%)	<0.0001†
1/4			9 (10.0%)		2 (3.3%)		7 (23.3%)	
2/4			11 (12.2%)		4 (6.7%)		7 (23.3%)	
3/4			25 (27.8%)		18 (30%)		7 (23.3%)	
4/4			44 (48.9%)		36 (60%)		8 (26.7%)	
Table 1 continued								
Right atrium major axis		90	63 ± 13	60	63 ± 13	30	65 ± 13	0.453*
Right ventricular diameter		71	44 ± 12	45	46 ± 12	26	42 ± 12	0.258*

Table 1 continued

TAPSE		33	16 ± 6	20	18 ± 5	13	13 ± 6	0.008*
RV function								
normal	n (%)	89	54 (60.7%)	59	35 (59.3%)	30	19 (63.3%)	0.976†
lightly impaired			15 (16.9%)		10 (16.9%)		5 (16.7%)	
moderately impaired			17 (19.1%)		12 (20.3%)		5 (16.7%)	
severely impaired			3 (3.4%)		2 (3.4%)		1 (3.3%)	
Tricuspid regurgitant gradient	mean±SD	68	30.2±13.3	45	31.6±13.6	23	27.6±12.7	0.255*
LV Ejection Fraction	mean±SD	86	57.8±5.9	57	58.4±5.2	29	56.8±6.9	0.264*
Mortality								
30-day	n	92	7 (7.9 %)					
3-month	n	92	13 (15.2 %)					
5-year	n	92	20 (25.7 %)					

AF, Atrial fibrillation; BMI, Body mass index; MI, myocardial infarction; NYHA, New York Heart Association functional class; PAP, pulmonary artery pressure; PH, pulmonary hypertension; RAP, right atrial pressure; RVP, right ventricular pressure; SD, standard deviation; TV, tricuspid valve.

*T-test. †Pearson's Chi-Square test. ‡Fishers' Exact test.

Table 2 Indications for Valve Surgery, Degree of Emergency, and Type of TV Surgery in the Total Population and in the Two Surgical Groups.

	Total N (%)	First TV surgery N (%)	TV reoperation N (%)
Total	92 (100%)	61 (100%)	31 (100%)
Primary TV disease:			0 (0%)
- Carcinoid tumour	2 (2.2%)	2 (3.3%)	
- Ebstein's anomaly	6 (6.5%)	6 (9.8%)	0 (0%)
- TV endocarditis	8 (8.7%)	6 (9.8%)	2 (6.5%)
- Rheumatic valve disease	12 (13.0%)	9 (14.8%)	3 (9.7%)
Secondary TV disease:			
- Secondary annular dilatation	38 (41.3%)	33 (54.1%)	5 (16.1%)
Traumatic TR	5 (5.4%)	5 (8.2%)	0 (0%)
Prosthetic valve dysfunction	21 (22.8%)	0 (0%)	21 (67.7%)
Elective	37 (40.2%)	22 (36.1%)	15 (48.4%)
Low emergency	47 (51.1%)	32 (52.5%)	15 (48.4%)
High emergency	3 (3.3%)	2 (3.3%)	1 (3.2%)
Salvage	1 (1.1%)	1 (1.6%)	0 (0%)
Annuloplasty (DE Vega)	8 (8.7%)	8 (13.1%)	0 (0.0%)
Annuloplasty + ring	25 (27.2%)	22 (36.1%)	3 (9.7%)
Valve replacement	59 (64.1%)	31 (50.8%)	28 (90.3%)
Bioprosthesis	33 (35.9%)	24 (39.3%)	9 (29%)
Mechanical valve	26 (28.3%)	7 (11.5%)	19 (61.3%)

N, Number; TR, tricuspid regurgitation; TV, tricuspid valve.

Identification of Predictors of Outcome after TV Surgery

For the entire cohort, univariable Cox proportional hazards analysis revealed that age ($p<0.0001$), extracardiac vascular disease ($p=0.001$), renal function ($p=0.022$), NYHA functional class 1-2 compared to NYHA 3-4 ($p=0.010$), and use of loop diuretics ($p=0.017$) or potassium-sparing diuretics ($p=0.002$) were significantly associated with

outcome. Whether valve repair or valve replacement was performed did not influence outcome (HR=0.722 (0.346-1.510); p=0.387). Similarly, whether valve replacement was performed with a bioprosthesis compared to a mechanical valve did not influence outcome (HR=0.691 (0.301-1.587); p=0.384). Hemodynamic parameters associated with outcome were right atrial pressure (p=0.004); right ventricular systolic and diastolic pressure (p=0.038 and p=0.043 respectively); and systolic, diastolic, and mean PAP (p=0.003; p=0.015; p=0.005, respectively). (Table 4) The only echocardiographic parameter that was associated with outcome was the tricuspid regurgitant gradient (p=0.027). Multivariable Cox proportional hazards analysis identified age (HR=1.089 (1.054-1.165); p=0.015) and NYHA functional class 1-2 vs. 3-4 (HR 6.671 (1.154-38.551); p=0.034) as factors significantly associated with outcome. (Table 5)

When patients presented in NYHA functional class 3 or 4, survival was significantly worse compared to patients presenting in NYHA functional class 1 or 2. Thirty-day, 90-day and 5 year survival was 100%, 100%, 94.7% respectively for NYHA class I and II whereas survival was 88.8%, 79.1% and 66.9% respectively for NYHA class III and IV (log-rank test, p=0.005). (Figure 2)

There was a significant interaction between mean PAP and the age-categories (HR 0.921 (0.839-1.011); p= 0.084). Only for the younger age group (<59 years of age), mean PAP was associated with the worse outcome (HR 1.090 (1.012-1.175); p=0.024). In the younger age group, thirty-day, 3 month, 5 year survival was 100%, 100%, 100% respectively for mean PAP < 25 mmHg whereas survival was 100%, 90%, 80% respectively for mean PAP ≥ 25 mmHg (log-rank test, p=0.008). PH didn't influence the survival of patients in the older age group (log-rank test, p=0.485) (Figure 3).

Table 3 Postoperative Complications in the population and in the two surgical Groups

Postoperative complication	Total N=92	First TV surgery N=61	TV reoperation N=31	P-value
Reoperation				
Tamponade	6 (6.5%)‡	4 (7%)§	2 (6.7%)‖	1*
Bleeding	12 (13%)	8 (13.1%)	4 (12.9%)	1*
Valve dysfunction	10 (10.9%)	7 (11.5%)	3 (9.7%)	1*
Postoperative MI	1 (1.1%)	0 (0%)	1 (3.2%)	0.337*
Infection (sternal/sepsis)	7 (7.6%)	5 (8.2%)	2 (6.5%)	1*
CVA/TIA	3 (3.3%)	1 (1.6%)	2 (6.5%)	0.262*
Pulmonary event	15 (16.3%)	10 (16.4%)	5 (16.1%)	0.974†
+ mechanical ventilation	14 (15.2%)	10 (16.4%)	4 (12.9%)	0.766*
Renal failure	12 (13.0%)	9 (14.8%)	3 (9.7%)	0.745*
+ dialysis	11 (12.0%)	9 (14.8%)	2 (6.5%)	0.323*
Postoperative high grade AV block	14 (15.2%)	5 (8.2%)	9 (29.0%)	0.013*
Postoperative definitive pacemaker	11 (12%)	4 (6.6%)	4 (6.6%)	0.039*
Arrhythmia (atrial and ventricular)	22 (25.3%)‡	14 (23%)§	8 (26.7%)‖	0.830†
Pleural effusion	9 (10.3%)‡	6 (10.5%)§	3 (10.0%)‖	1*

AV, atrioventricular; CVA, cerebrovascular accident; MI, myocardial infarction; TIA, transient ischemic attack; TV, tricuspid valve. *Fishers' Exact test. †Pearson's Chi Square test. ‡Statistics were calculated on n=87. §Statistics were calculated on n=57. ‖Statistics were calculated on n=30.

Figure 2 Kaplan-Meier curve showing survival stratified by NYHA functional class. Survival in patients presenting in NYHA functional class 3 or 4 was significantly worse compared to patients presenting in NYHA functional class 1 or 2. Thirty-day, 90-day and 5 year survival was 100%, 100%, 94.7% respectively for NYHA class I and II whereas survival was 88.8%, 79.1% and 66.9% respectively for NYHA class III and IV (log-rank test, p=0.005). NYHA: New York Heart Association.

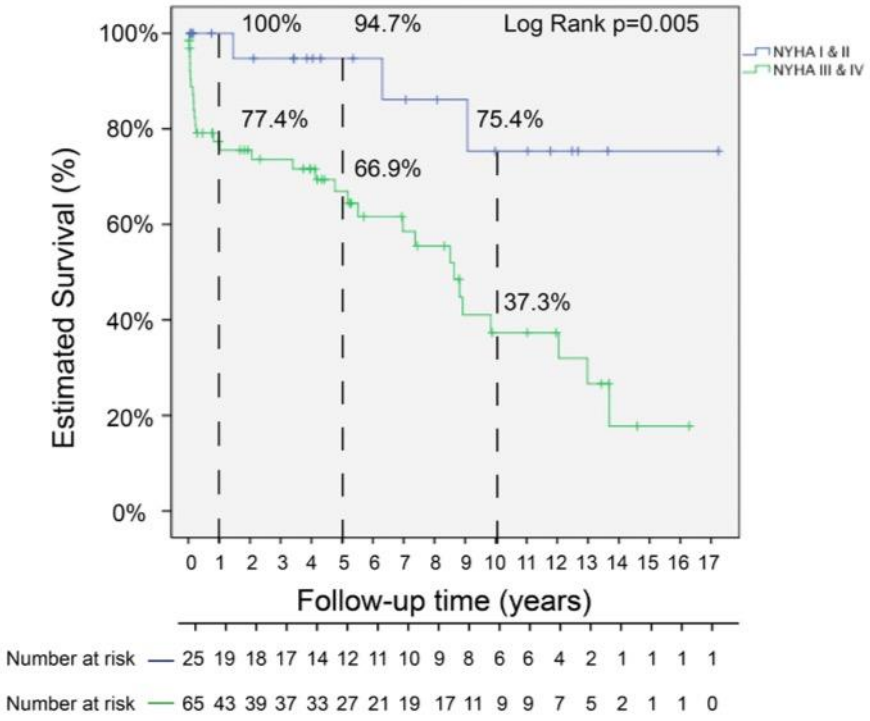


Table 4 Univariable Cox regression for all-cause mortality. Evaluation of demographic, echocardiographic and hemodynamic parameters.

	N	*P-value*	*HR (95% CI)*		*N*	*P-value*	*HR (95% CI)*
Demographics				**Medical treatment**			
Age (years)	92	< 0.0001*	1.071 (1.035-1.108)	Loop diuretics	88	0.017*	2.980 (1.212-7.327)
Gender	92	0.079	0.492 (0.223-1.086)	Potassium sparing diuretics	88	0.002*	3.868 (1.665-8.985)
BMI (kg/m^2)	91	0.344	0.959 (0.880-1.046)	ACE-I or ARB	88	0.767	1.118 (0.535-2.338)
Cardiac risk profile	88	0.510	1.098 (0.831-1.450)	Beta-blockade	88	0.954	1.021 (0.498-2.095)
Extracardiac vascular disease	92	0.001*	4.961 (1.865-13.200)	**Echocardiography**			
Previous cardiac surgery	92	0.803	1.099 (0.524-2.304)	TR (0-4/4)	90	0.510	0.904 (0.669-1.221)
Recent MI (<90 days)	83	0.420	1.815 (0.426-7.735)	RV diameter	71	0.825	0.996 (0.961-1.033)
Angina pectoris	89	0.479	0.649 (0.196-2.152)	RV function (normal-severe impairment)	89	0.975	0.994 (0.688-1.436)
Chronic lung disease	91	0.064	2.309 (0.951-5.605)	RA major	90	0.723	1.055 (0.977-1.034)
Renal failure	92	0.022*	1.725 (1.081-2.751)	Tricuspid regurgitant gradient	68	0.027*	1.031 (1.004-1.060)
Cardiac rhythm	92	0.543	1.138 (0.751-1.722)	LV Ejection Fraction	86	0.597	0.987 (0.941-1.035)
NYHA 1-2 vs. NYHA 3-4	90	0.010*	4.733 (1.444-15.508)	**Hemodynamics**			
First TV surgery vs. TV reoperation	92	0.341	0.704 (0.341-1.452)	RAP (mmHg)	65	0.004*	1.122 (1.037-1.213)
Type of TV surgery	92	0.779	1.071 (0.666-1.722)	RVP_{syst} (mmHg)	65	0.038*	1.030 (1.002-1.059)

Table 4 continued							
annuloplasty versus replacement	33	0.387	0.722 (0.346-1.510)	RVP_{diast} (mmHg)	64	0.043*	1.081 (1.002-1.167)
Bioprosthesis versus mechanical valve	59	0.384	0.691 (0.301-1.587)	PAP_{syst} (mmHg)	69	0.003*	1.038 (1.013-1.063)
Urgency grade	88	0.713	0.882 (0.452-1.723)	PAP_{diast} (mmHg)	69	0.015*	1.076 (1.015-1.141)
EuroScoreII	92	0.002*	1.119 (1.041-1.204)	PAP_{mean} (mmHg)	63	0.005*	1.061 (1.018-1.106)

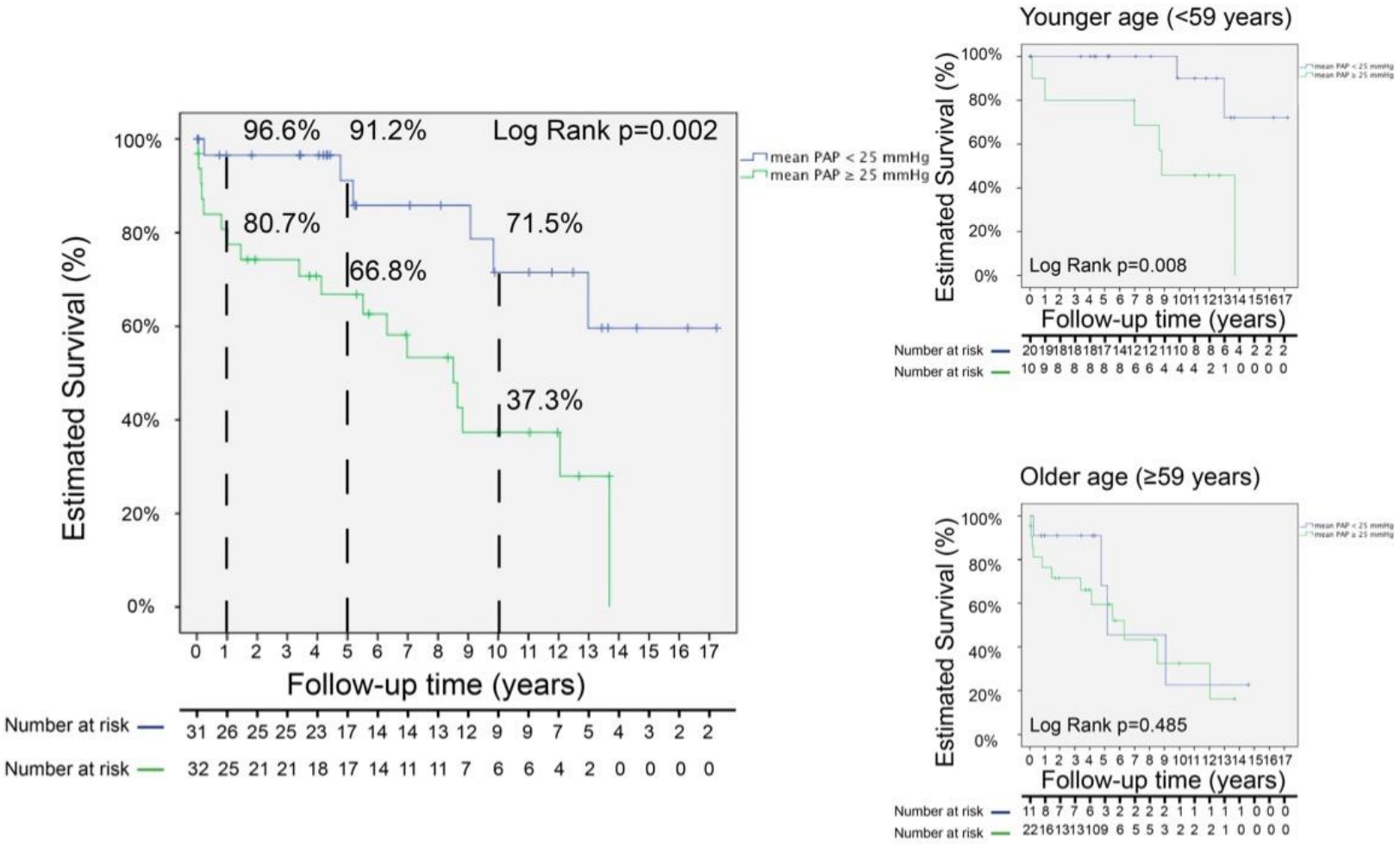
BMI, Body mass index; MI, myocardial infarction; NYHA, New York Heart Association functional class; PAP, pulmonary artery pressure; RAP, right atrial pressure; RVP, right ventricular pressure; TV, tricuspid valve. * $P<0.05$; † P for interaction <0.10.

Table 5 Multivariable Cox Regression for all-cause mortality.

	N	***P-value***	***HR (95% CI)***
Age	60	0.015*	1.089 (1.054-1.165)
NYHA 1-2 vs. 3-4		0.034*	6.671 (1.154-38.551)
Extracardiac vascular disease		0.095	5.696 (0.739-43.909)
Renal failure		0.227	1.699 (0.719-4.011)
First TV surgery vs. TV reoperation		0.500	1.389 (0.535-3.609)
EuroscoreII		0.177	0.903 (0.779-1.047)
PAP_{mean}		0.984	0.999 (0.945-1.057)
Loop diuretics		0.191	2.619 (0.619-11.094)

NYHA: New York Heart Association functional class; TV: tricuspid valve; PAP: pulmonary artery pressure. *P<0.05.

Figure 3 Kaplan-Meier curve showing survival in the younger (<59 years of age) and older groups, stratified by mean PAP (≥ 25 mmHg). In the younger age group, thirty-day, 3 month, 5 year survival was 100%, 100%, 100% respectively for mean PAP < 25 mmHg whereas survival was 100%, 90%, 80% respectively for mean PAP ≥ 25 mmHg (log-rank test, p=0.008). PAP: pulmonary artery pressure



Discussion

This study showed that isolated TV surgery in present-day practice is still associated with significant postoperative and long-term mortality. In this study sample, no difference between first TV surgery and reoperation of the TV was observed. Age and NYHA functional class appear to influence outcome while PH is only associated with the worse outcome in younger patients (<59 years of age).

Short-term and long-term mortality in the studied cohort of patients is high. The postoperative mortality of 7.9% is comparable to that reported in contemporary series.[3, 17] However, different studies report varying mortality rates depending on the studied population. It should be noted that the indication for surgery and whether combined surgery is performed greatly influences outcome.[16, 22, 23] Carcinoid disease is associated with a postoperative mortality of 60%.[24] For comparison, TV repair for primary structural TV disease has a postoperative mortality of only 4%.[15] Together, this suggests that TV dysfunction results from a diverse pathology that originates because of several diseases with different hemodynamic and functional properties.[25] However, in our series we could not identify indication of surgery as a predictor of outcome, probably because of the diversity of our dataset. Unfortunately, we were not able to compare the outcomes of our surgical group with a matched control group in whom severe TR was treated medically. We believe that this aspect should be studied prospectively in the future.

NYHA functional class is a known predictor of mortality in TV surgery, as confirmed by our dataset.[13, 26, 27] We report excellent survival in patients who present in NYHA functional class 1 and 2 pre-operatively. Postponing surgery until symptoms occur is associated with the worse outcome.[11, 12, 28] On the other hand, when patients are asymptomatic, surgery can be performed at a low operative risk.[11] Furthermore, age itself seems to be a very important and statistically independent predictor of outcome in patients undergoing TV surgery.[29, 30] Therefore, our data support the approach of intervening at a younger age, when symptoms of TV disease are absent or minimal.

Although current guidelines do not advise routine intervention for asymptomatic isolated moderate to severe TV pathology, long-standing volume overload of the right ventricle is associated with increased stroke work, structural changes of the right ventricle and valvular apparatus, and eventually the development of right ventricular

failure.[31-34] These morphological and functional changes might explain the low success rate of surgery when performed at later stages of the disease, when changes are irreversible. RV function has been identified as a predictor of outcome.[12, 35] Unfortunately, our pre-operative echocardiographic data failed to show an association between RV function and outcome. Reason for this could be that 2D echocardiographic evaluation of the RV is difficult and often inaccurate compared to other imaging techniques such as magnetic resonance. Also, RV end-diastolic pressure as determined by right heart catheterization were associated with outcome and could be a better marker of RV dysfunction. On the other hand, significant remodelling of the right heart after TV surgery can occur. It has been shown that RV geometry and RV ejection fraction improve after surgery.[36] The evolution of RV geometry and function after surgery might therefore be more important than the pre-operative evaluation. In these series remodelling of the right ventricle after surgery could not be evaluated because of the lack of echocardiographic follow-up data within a narrow time frame.

We also studied whether invasive pulmonary hemodynamic data such as PAP affect outcome. Controversy exists on the use of invasive hemodynamic assessment during the preoperative evaluation of valvular heart disease.[1] Indeed, an invasive approach is currently not recommended in guidelines, although a pressure-load on the right ventricle is associated with worse outcome in different heart disease. Mean PAP is the most reproducible measurement in invasive assessment of pulmonary hemodynamics as it is less dependent on adrenergic state and volume-overload. When included in the univariable regression analysis on the entire dataset (i.e., no age stratification), increasing mean PAP was related to worse outcome; however, multivariable analysis revealed that age and NYHA functional class were more important.[29, 30] PAP tends to increase with age and in our dataset a significant interaction between age and PAP was noted.[21] Indeed, in the younger population PH seems to influence prognosis while no significant association of PH with outcome was observed in the older age group. We hypothesize that the persisting pressure-load on the right ventricle in patients with PH in time impairs right ventricular function. Furthermore, it is possible that once PH occurs, the optimal window for performing TV surgery has closed.

It is generally accepted that patients who undergo a second cardiovascular intervention by median sternotomy have a higher operative risk. Redo surgery is a risk

factor in many established risk scores.[18] In this study sample, TV reoperation did not have a higher mortality when compared to first TV operation. However, 43% of the patients with a first tricuspid valve intervention already underwent previous sternotomy and thus presented with an operative risk, similar to the patients who underwent TV reoperation. This might explain the similar outcome in both groups. Moreover, because of the observational nature of the study, a selection bias could have occurred as reoperation is generally reserved to the patients that are considered to have the better prognosis. Nevertheless, both study groups were equally matched in baseline characteristics, except for the EuroScore II, which was even higher in the TV reoperation group. Our data suggest that the general preoperative state of a patient might be more important than technical difficulties related to the surgery itself.

Limitations

We present observational data from a single institution. At inclusion, no randomization was performed and patients were referred for cardiac surgery after multidisciplinary consultation based on current guidelines and best medical practice. Therefore these results should be interpreted with caution, as a potential selection bias is not excluded. Furthermore, because isolated TV surgery is rarely performed, the studied number of patients is relatively low. Nevertheless, to our knowledge, we present the largest patient population undergoing isolated tricuspid valve surgery. A multicentre registry could possibly overcome these shortcomings especially when all institutions follow the same registry protocol.

Conclusions

Isolated TV surgery is still associated with important postoperative and long-term mortality, both for first TV surgery and TV reoperation. Pre-operative NYHA functional class and, in younger patients, pulmonary hypertension appear to determine prognosis.

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2. Additional tricuspid annuloplasty in mitral valve surgery results in better clinical outcome: a propensity matched analysis.

Abstract

Objective

The clinical benefit of tricuspid annuloplasty (TA) in patients undergoing mitral valve surgery (MVS) is still debated. We evaluated the immediate surgical success of MVS with or without TA, post-operative outcome and the medium-term additional effect of TA.

Methods

Patients undergoing MVS with or without TA between 09-2003 and 12-2009 were included and were followed until 09-2013 to achieve a median follow-up time of 5 years (IQ3.7-6.9). The endpoint of mortality due to cardiac causes and the combined end-point of cardiac mortality and hospitalisation for heart failure were evaluated. A propensity score was constructed for the chosen surgical strategy and included in the cox regression model to evaluate the clinical benefit of TA at the time of MVS.

Results

From 150 patients (84 female; age 67±12 years), 82 presented with tricuspid regurgitation (TR)<2/4 and underwent isolated MVS. Of 68 patients presenting with TR≥2/4, 31 underwent isolated MVS whereas 37 underwent additional TA.

In the patients with preoperative TR>2, TR was significantly reduced at 6-month follow-up when additional TA was done [mean TR reduction 1.13(SE0.20); p<0.0001].

Patients with preoperative TR≥2/4 had worse survival (log-rank p=0.009), compared to patients with TR<2, and in these patients, propensity score-adjusted event-free survival for the combined end-point was significantly better when concomitant TA was performed [Cox Regression HR 2.855(1.082-7.532); p=0.035].

Conclusion

Additional TA at the time of MVS is an effective surgical measure to reduce functional TR severity. Propensity-matched analysis shows a clinical benefit of this approach over isolated MVS in patients with preoperative TR≥2/4.

Introduction

Functional tricuspid regurgitation (TR) often accompanies mitral regurgitation (MR).[1] Although TR may be only mild at the time of surgery, TR severity progresses after isolated mitral valve surgery in ca. 30% of patients and can occur years after the initial left-sided surgery.[2-4] The complex pathophysiology of functional TR makes the natural history unpredictable.[1, 5, 6] Increasing TR severity is known to be associated with worse prognosis.[2, 7] Furthermore, reoperation for isolated TR is associated with a high perioperative, short- and long-term mortality whereas performing tricuspid annuloplasty at the time of mitral valve surgery (MVS) adds little time to the procedure.[8, 9] Therefore, a more liberal approach in performing tricuspid valve repair at the time of MV surgery is now advocated by both the ESC and the AHA/ACC guidelines on valvular heart disease.[10, 11]

Although such an approach results in favourable remodelling of the right ventricle and lesser recurrence of TR, data on clinical outcome are scarce. [4, 12, 13] Improved mid-term survival of concomitant tricuspid annuloplasty (TA) has been reported in patients with functional MR due to, mainly ischemic, cardiomyopathy.[14] However, the gross majority of MVS is performed for chronic degenerative valvular disease.[15] Comparison of the outcome in patients undergoing MV surgery with or without TA is notoriously difficult because the former often present in a worse clinical state with more severe TR, higher NYHA functional class and decreased right ventricular function.[4] Cross-sectional studies therefore failed to show improved outcome for patients undergoing simultaneous TA and MVS in the past. [16, 17]

The aim of our study was to assess the immediate surgical success of MVS with or without TA, to examine post-operative outcome and to evaluate the clinical benefit of

TA in the setting of MVS corrected for pre-operative parameters using a propensity score analysis.

Methods

Patient selection and data collection

From the institutional database of Cardiac Surgery at the University Hospitals Leuven, patients undergoing MVS were retrospectively included from September 2003 until December 2009 and followed until September 2013. All patients had their follow-up at the University Hospitals Leuven, a tertiary care center. Patients with primary tricuspid valve pathology, redo surgery or severe cardiac and non-cardiac disease other than valvular heart disease at the moment of inclusion were excluded.

Patients underwent either isolated MVS or MVS in combination with TA. Patients were divided into 3 groups: (1) patients with TR<2/4 undergoing isolated mitral valve surgery (Group TR-/MVS); (2) patients with TR≥2/4 undergoing isolated mitral valve surgery (Group TR+/MVS) and (3) patients with TR≥2/4 undergoing mitral valve surgery in combination with tricuspid annuloplasty (Group TR+/MVS+TA).

The mitral valve was repaired whenever feasible, otherwise, mitral valve replacement was performed. The decision to perform concomitant TA was taken after multi-disciplinary discussion by the institutions heart team. Demographic and clinical data as well as echocardiographic data were included. Post-operative data including echocardiography immediately post-operative and at 6-month follow-up were reviewed. Outcome for every patient was evaluated. The local ethics committee approved patient inclusion and analysis.

Endpoints

Cardiac mortality and the combined endpoint of cardiac mortality and hospitalisation for heart failure were evaluated for each group. Heart failure was defined as presentation in NYHA functional class III and higher, signs of sodium and water retention and echocardiographic evidence of fluid overload or elevated NT-proBNP.

Statistical analysis

Continuous data and categorical data are represented by means and standard deviation or frequencies and percentages, respectively.

First, pre-operative demographic data and echocardiographic data were analysed and compared between groups by unpaired t-test or Fisher's exact test where applicable.

Next, immediate surgical success was evaluated by comparison of pre-operative echocardiographic data with echocardiography directly post-operative and at 6 months post-operatively by paired t-test with Bonferoni-correction for multiple testing.

Third, the occurrence of cardiac mortality and the combined endpoint of cardiac mortality and hospitalisation for heart failure were evaluated for each group by Kaplan-Meier survival analysis.

Last, a non-parsimonious propensity score was constructed by multivariate binary logistic regression and the probability was calculated for each patient with TR $\geq$ 2/4 to be allocated by the heart team to concomitant tricuspid annuloplasty (Group TR+/MVS vs. Group TR+/MVS+TA). Based on current guidelines and practice in our hospital, age, preoperative NYHA functional class, TR severity, tricuspid annular diameter and preoperative tricuspid annular plane systolic excursion (TAPSE) were included in the model [C-statistic 0.861 (95%CI=0.767-0.956); Hosmer Lemeshow p=0.279].

Multivariate Cox regression was performed with the propensity score and the surgical approach as variables and propensity score-adjusted survival curves were plotted subsequently.

All tests were two-tailed. A P-value <0.05 was considered significant. Analyses were performed using SPSS® (version 22 SPSS, Chicago, USA).

Results

Patient inclusion

From September 2003 until December 2009, 882 patients underwent MVS at the University Hospitals Leuven. Of these, 625 were referred from and later followed outside the hospital. From the remaining 257 patients, 17 were lost to follow-up. Another 90 patients were excluded for various reasons as is summarized in **Figure 1**.

The study cohort comprised the remaining 150 patients. Follow-up was 100% complete. Median follow-up time was 5 years (IQ range 3.7-6.9).

Patient characteristics

Demographic, echocardiographic and post-operative data are listed in **Table 1**. Eighty-two patients had pre-operative TR<2/4 (group TR-/MVS). From the 68 patients with TR ≥ 2/4, 37 underwent concomitant tricuspid valve repair (group TR+/MVS+TA), and 31 patients underwent isolated mitral valve surgery (group TR+/MVS). Patients in group TR+/MVS+TA had significantly more TR and significantly lower TAPSE than patients in group TR+/MVS. The indication for surgery can be found in **Figure 2**.

In 82 (55%) patients, mitral valve repair was feasible. The other 68 (45%) patients underwent mitral valve replacement, in 37 (54%) cases with a mechanical prosthetic valve. The distribution of the surgical strategy was not significantly different across groups (Fisher's Exact p=0.518).

Of 37 patients undergoing additional tricuspid annuloplasty, 21 (56%) underwent De Vega annuloplasty and 16 (44%) underwent ring annuloplasty.

Figure 1 Flow chart to identify patients eligible for analysis

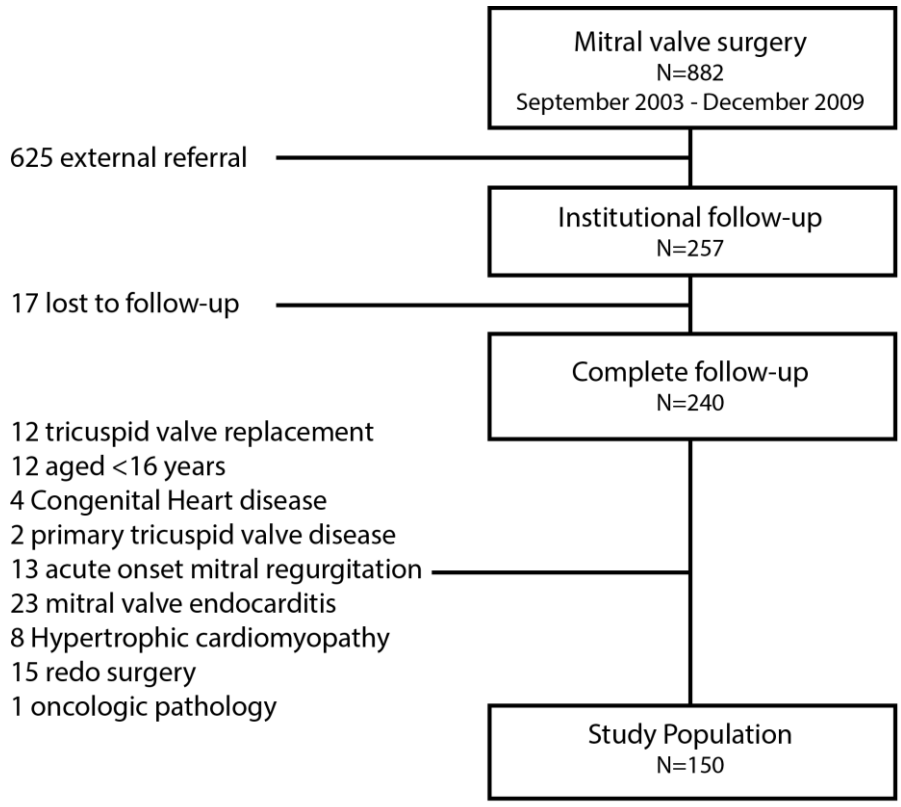
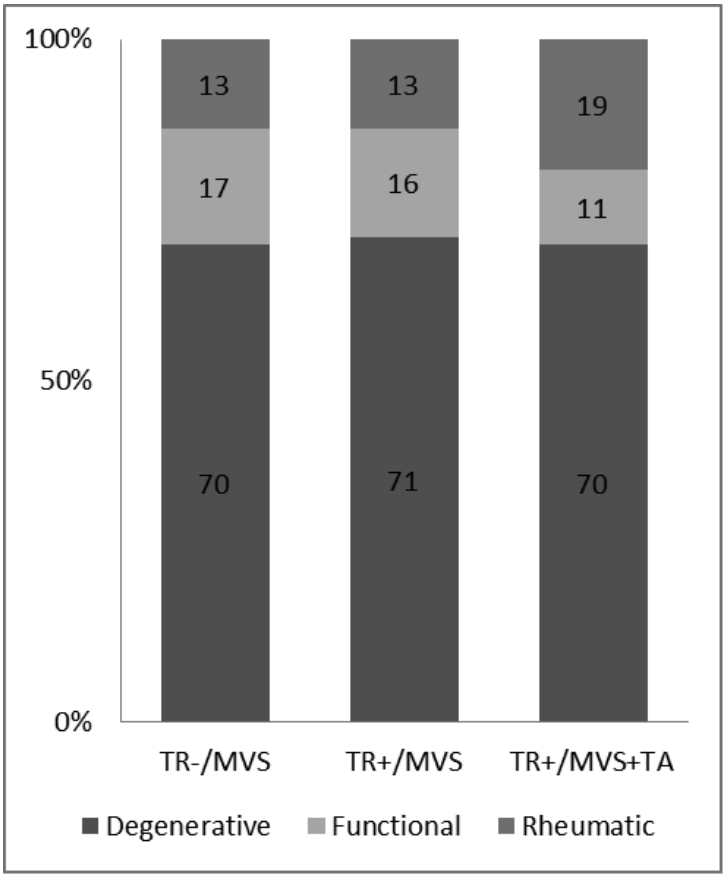


Figure 2 Indication for surgery expressed as percentage of total within each group.



Immediate surgical success after mitral and tricuspid valve surgery

Significant reduction of MR was observed in all patients early post-operatively and at 6 months follow-up. Results are summarized in **Table 2**. In patients presenting without significant TR (Group TR-/MVS), TR post-operatively was slightly but significantly increased ($p<0.001$ immediately post-operatively and $p=0.018$ at 6 months), albeit still in what is considered to be the physiological range. In Group TR+/MVS, small but significant decrease of TR could be seen directly post-operatively. This decrease did not persist 6 months post-operatively. Patients undergoing simultaneous tricuspid and mitral valve surgery presented with a large and significant decrease of TR post-operatively. This improvement persisted at 6 months follow-up.

NYHA functional class was significantly better compared to pre-operatively in all patients, alive at 6 months follow-up.

Table 1 Demographic, pre-operative echocardiographic parameters and post-operative variables in Group TR-/MVS; Group TR+/MVS and Group TR+/MVS+TA.

		TR-/MVS		TR+/MVS		TR+/MVS+TA		**p 2 vs. 3**
Demographics		n		n		n		
Gender	n female (%)	82	42 (51%)	31	17 (55%)	37	27 (73%)	§0.135
Age (years)	mean (±SD)	82	64 (±12)	31	72 (±8)	37	70 (±11)	0.383
BMI (kg/m^2)	mean (±SD)	82	26.8 (±5.4)	31	26.1 (±3.8)	37	24.7 (±4.2)	0.146
Creatinine (mg/dL)	mean (±SD)	81	1.22 (±1.15)	31	1.22 (±0.42)	37	1.18 (±0.32)	0.634
NYHA functional class	mean (±SD)	82	2.2 (±0.9)	31	2.5 (±0.8)	37	2.6 (±0.7)	0.741
Atrial fibrillation	n (%)	82	30 (36.6%)	31	18 (58.1%)	37	25 (67.6%)	§0.004*
Pacemaker	n (%)	82	3 (3.7%)	31	1 (3.2%)	37	1 (2.7%)	§1
Echocardiography								
Mitral Regurgitation (x/4)	mean (±SD)	81	3.1 (±0.6)	31	3.2 (±0.7)	37	3.1 (±0.6)	0.622
Tricuspid Regurgitation (x/4)	mean (±SD)	82	1.06 (±0.47)	31	2.3 (±0.4)	37	2.6 (±0.8)	0.018*
RV-RA gradient (mmHg)	mean (±SD)	81	29 (±9)	31	43 (±13)	37	37 (±14)	0.179
LVEDD (mm)	mean (±SD)	73	52 (±10)	31	51 (±12)	37	51 (±9.6)	0.996
LVEF (%)	mean (±SD)	79	60 (±13)	31	62 (±12)	37	59 (±12)	0.385
RV diameter (mm)	mean (±SD)	68	29 (±5)	31	31 (±7)	37	33 (±6)	0.412
RV annular diameter (mm)	mean (±SD)	62	30 (±5)	31	32 (±7)	37	34 (±6)	0.412
TAPSE (mm)	mean (±SD)	54	22 (±5)	31	23 (±4)	37	18 (±4)	<0.0001*
Post-operative								
30-day all-cause mortality	n (%)	82	2 (2.4%)	31	3 (9.7%)	37	0 (0%)	§0.090
3-month all-cause mortality	n (%)	82	3 (3.7%)	31	4 (12.9%)	37	2 (5.4%)	§0.400
Duration ITE stay (days)	mean (±SD)	82	5 (±8)	28	6 (±12)	36	6 (±9)	0.829
Duration hospitalisation(days)	mean (±SD)	80	18 (±18)	28	19 (±17)	35	26 (±39)	0.399
New onset atrial fibrillation	n (%)	52	18 (34.6%)	13	4 (30.8%)	12	4 (33.3%)	§1
New permanent pacemaker	n (%)	79	12 (15.2%)	30	3 (10%)	36	10 (27.8%)	§0.153

BMI= body mass index; RV=right ventricle; LVEDD=left ventricular end-diastolic diameter; LVEF=left ventricular ejection fraction; TAPSE=tricuspid annular plane systolic excursion. *p<0.05=significant.

Table 2 Procedural success of surgery across groups. Mitral regurgitation was reduced in all study groups. TR was only significantly decreased at 6 months in patients undergoing tricuspid annuloplasty. TR+ indicates TR≥2/4 preoperatively. MVS indicates isolated mitral valve surgery. MVS+TA indicates additional tricuspid annuloplasty. Note: 8 patients didn't have echocardiography at 6 months follow-up.

	TR-/MVS			TR+/MVS			TR+/MVS+TA		
	N	Mean	t-test	N	Mean	t-test	N	Mean	t-test
MR									
Preop	82	3.11 (±0.63)		31	3.21 (±0.67)		37	3.14 (±0.57)	
Postop	80	0.44 (±0.71)	<0.0001*	29	0.48 (±0.74)	<0.0001*	36	0.68 (±0.81)	<0.0001*
6months	78	0.71 (±0.87)	<0.0001*	24	0.71 (±0.91)	<0.0001*	34	0.88 (±0.78)	<0.0001*
TR									
Preop	82	1.06 (±0.47)		31	2.27 (±0.44)		37	2.65 (±0.80)	
Postop	80	1.44 (±0.84)	0.0001*	29	1.78 (±0.86)	0.0388*	36	1.15 (±0.74)	<0.0001*
6months	78	1.30 (±0.85)	0.0185*	24	1.90 (±0.92)	0.2204	34	1.46 (±0.91)	<0.0001*
NYHA									
Preop	82	2.2 (±0.9)		31	2.5 (±0.8)		37	2.6 (0.7)	
6months	78	1.5 (±0.7)	<0.0001*	26	1.7 (±0.9)	<0.0001*	35	1.6 (±0.7)	<0.0001*

Short- and medium-term clinical outcome after mitral and tricuspid valve surgery

Early post-operative all-cause mortality at 30 days and 3 months was 3.3% and 6% respectively.**(Table 1)** Event-rate for the combined endpoint of cardiac mortality and hospitalisation for heart failure, for cardiac mortality and for hospitalisation for heart failure can be found in **Table 3**.

Event free survival was significantly better in patients presenting without significant preoperative TR (<2/4), compared to patients with preoperative TR > 2 (30-day cardiac mortality=2.4% vs 4.4%; 1-year=3.7% vs 10.6%; 5-year=7% vs 22.3%; Log Rank p=0.009). In unadjusted analysis, there was no difference in cardiac mortality between patients with TR≥2/4 undergoing isolated mitral valve surgery (Group TR+/MVS) and patients undergoing additional tricuspid annuloplasty (Group

TR+/MVS+TA) (30-day cardiac mortality=9.7% vs 0%; 1-year=16.1% vs 5.6%; 5-year=24.6% vs 20.3%; Log Rank p=0.414). **(Figure 3)**, whereas a trend towards better outcome for the combined endpoint of cardiac mortality and hospitalisation for heart failure in the TR+/MVS+TA group could be seen (30 day event-rate=9.7% vs 0%; 1-year=29% vs 5.6; 5-year=57.2 vs 39.4%; Log Rank p=0.077).

When incorporating the propensity score into a multivariable Cox regression model, no significant benefit in cardiac mortality of additional TA in patients with preoperative TR≥2/4 could be observed [HR 2.9 (0.8-10.7); p=0.108], whereas propensity score-adjusted event-free survival for the combined endpoint of cardiac death and hospitalisation for heart failure was significantly better for patients with preoperative TR >2 undergoing additional TA [HR 2.9 (1.1-7.5); p=0.034]. **(Figure 4)**

Table 3 Medium-term event-rate for each group studied. The combined endpoint was composed of cardiac death and hospitalisation for heart failure.

	TR-/MVS	TR+/MVS	TR+/MVS+TA
Combined endpoint			
30 days	3 (4%)	3 (10%)	0 (0%)
1 year	10 (12%)	9 (29%)	2 (6%)
5 years	17 (22%)	16 (57%)	13 (39%)
Cardiac-related death			
30 days	2 (2%)	3 (10%)	0 (0%)
1 year	3 (4%)	5 (16%)	2 (6%)
5 years	5 (7%)	7 (25%)	7 (20%)
Hospitalization for heart failure			
30 days	1 (1%)	0 (0%)	0 (0%)
1 year	7 (9%)	4 (13%)	0 (0%)
5 years	12 (15%)	9 (33%)	6 (19%)

Figure 3

Unadjusted event-free survival for **(A)** Cardiac mortality and **(B)** Cardiac mortality and hospitalisation for heart failure.

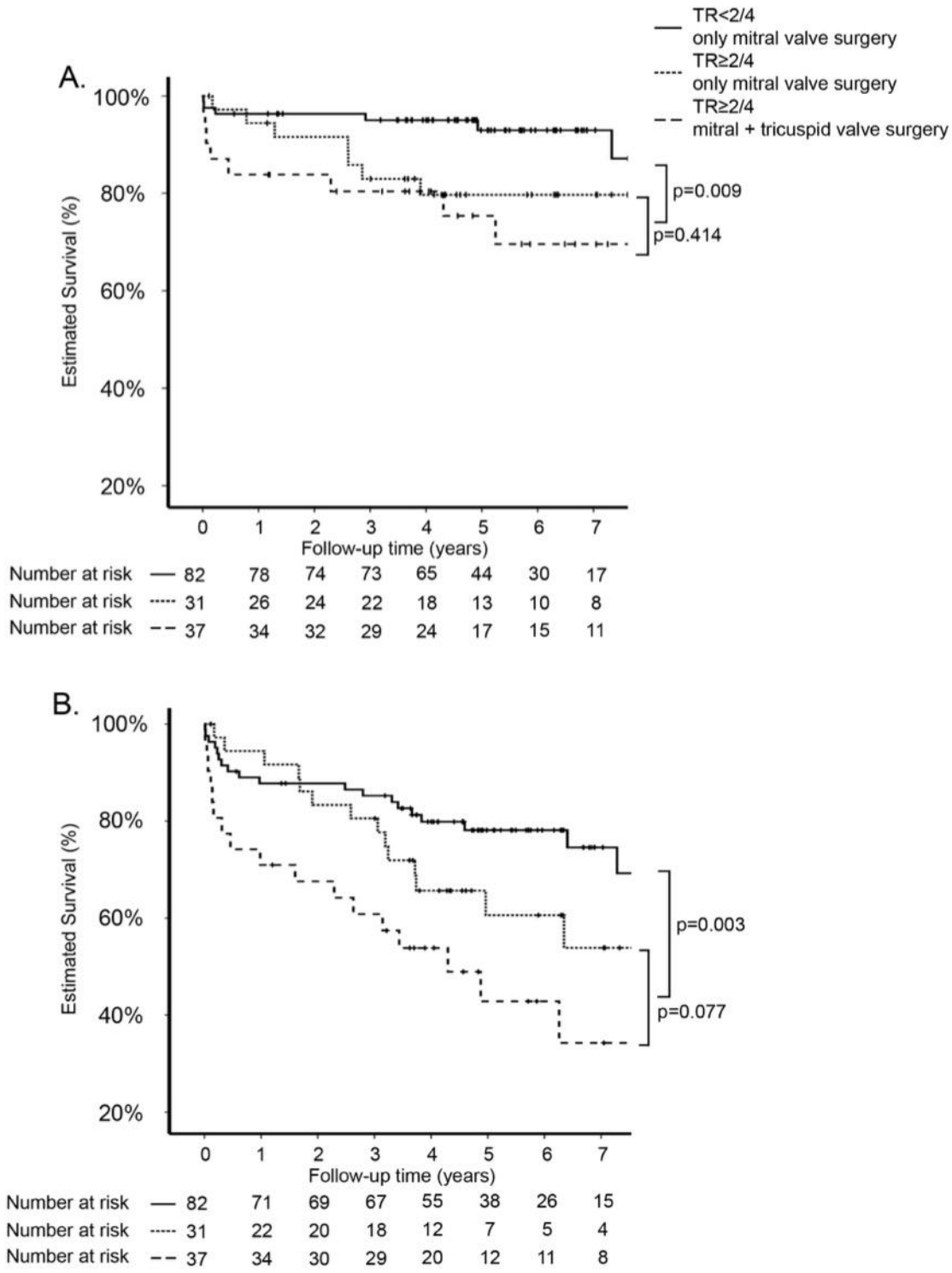
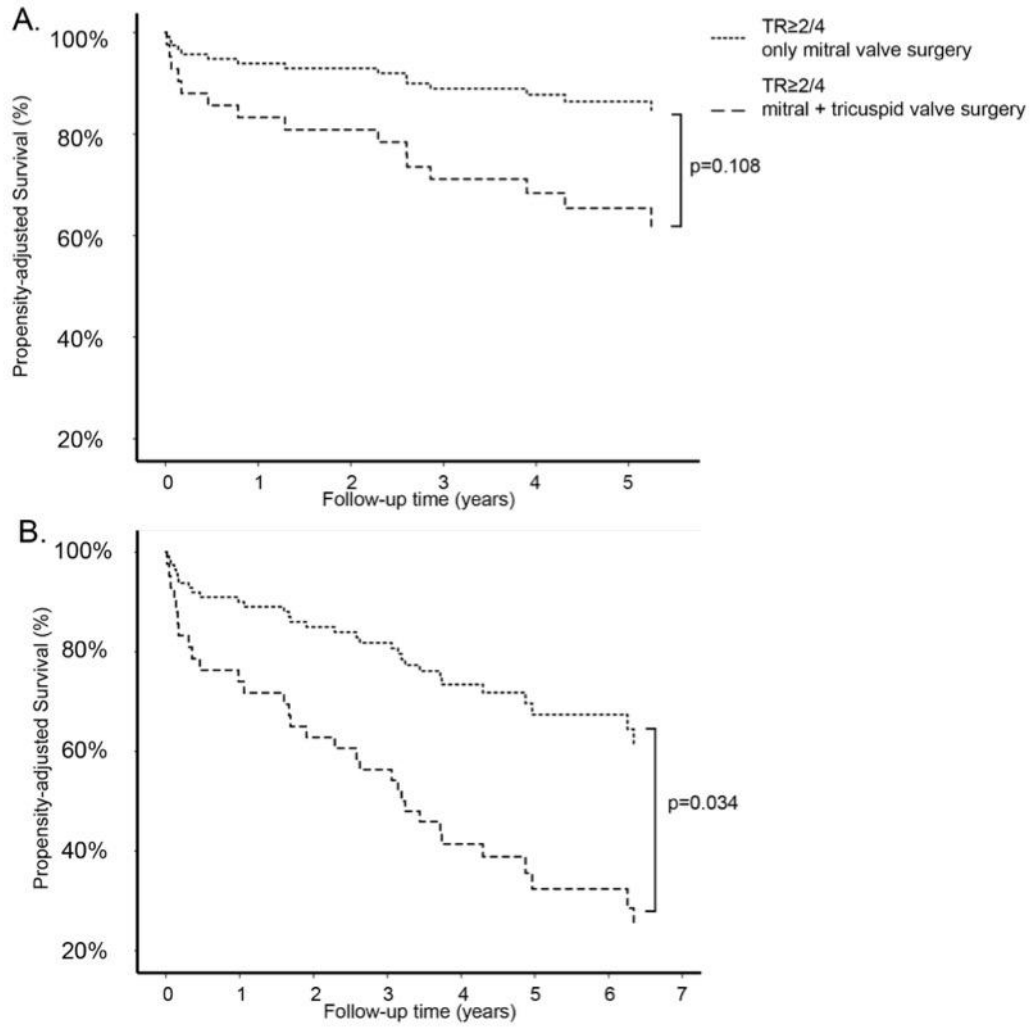


Figure 4 Propensity matched adjusted event-free survival for **(A)** cardiac mortality and **(B)** Cardiac mortality and hospitalisation for heart failure in patients with significant preoperative functional tricuspid regurgitation (TR ≥2/4).



Discussion

This study shows that additional tricuspid annuloplasty at the time of MVS significantly reduces TR severity postoperatively. Patients with TR ≥ 2/4 who undergo simultaneous MVS and TA have an improved event-free survival for the combined endpoint of cardiac mortality and hospitalisation for heart failure.

The value of tricuspid annuloplasty with MVS is still debated. However, both the European and American guidelines on valvular heart disease have implemented indications for concomitant tricuspid annuloplasty at the time of MVS in their recommendations.[10, 11] TR severity, tricuspid annular diameter and right ventricular

function are all important factors in the decision process whether the tricuspid valve has to be repaired at the time of MVS. Some authors even advocate tricuspid annuloplasty in the absence of preoperative TR to prevent progression of TR in the long term.[18, 19]

Increased pulmonary arterial pressure, right ventricular and TV annular dimensions contribute independently to functional TR.[1, 20-23] Although surgery of the MV can reduce the increased pulmonary arterial pressure caused by chronic MR, the structural alterations at the level of the right ventricle often persist after isolated MVS.[24, 25] Also, in degenerative MR, disease of the fibrous skeleton could be progressive and causative for the further deterioration of the valvular function, especially of the "untreated" tricuspid valve.[23] Because of this, it is clear that TR doesn't resolve after isolated MVS and even progresses after successful left-side valve surgery.[2] Progression or persistence of TR in the setting of MVS occurs frequently and is associated with worse prognosis.[2-4] If we aim to reduce TR and prevent the development of TR, TA should be considered at the time of MVS. The durability of TA in the setting of mitral valve disease has been shown in other published series.[26] Our data show successful reduction of MR severity and NYHA functional class in all surgical-treated patients. However, when preoperative TR was present, there was no significant reduction of TR at 6 months follow-up when the tricuspid valve was left untreated. On the other hand, persistent reduction of TR at 6 months was noted in the patient group undergoing tricuspid annuloplasty.

Although TA successfully reduces TR, the net clinical benefit of performing simultaneous tricuspid valve surgery is unclear.[26] In patients with functional MR, mainly due to ischemic cardiomyopathy, 5-year mortality was lower in patients undergoing TA at the time of mitral valve repair.[14] These data were adjusted for left ventricular parameters, as possible confounders of outcome. Opposed to this, several studies failed to show that tricuspid annuloplasty is beneficial in patients with other causes of MR.[16, 17] As the majority of MR occurs due to reasons other than ischemic cardiomyopathy, the true benefit of TA remains to be proven.

In addition, a registry including post-operative results in 17 centers showed a higher mortality and an increased operative time in patients undergoing additional TA.[27] Furthermore, we observed a higher but not significant incidence of permanent

pacemaker implantation in the TR+/MVS+TA group compared to the TR+/MVS group (27.8% vs 10%; p=0.153). On the other hand, additional TA was not associated with higher post-operative mortality in our study sample and no increased mortality was reported in studies from centers where a liberal approach towards tricuspid annular repair is practiced.[4, 8, 9]

A comparison of both surgical approaches is hampered by the heterogeneity of patients. The decision to operate on the tricuspid valve concomitantly with the mitral valve is taken by multi-disciplinary consultation by the institution's heart team. This often results in proposing the combined approach in "sicker" patients with already decreased right ventricular function, more dilated tricuspid valve annulus, more severe TR and in higher NYHA functional class. These are all known determinants of worse post-operative outcome. [4, 8, 9] To adjust for possible confounders, we calculated the probability for allocation to one of the surgical approaches for each patient. After adjustment, an improved event-free survival for the combined end-point of cardiac mortality and hospitalisation for heart failure could be shown in patients undergoing MVS with TA (Group TR+/MVS+TA).**(Figure 4)** The better event-free survival for patients undergoing simultaneous TA is mainly due to a lower number of hospitalisations for heart failure.**(Table 3)** The volume-load associated with TR increases stroke work of the right ventricle and impairs ventricular interdependence.[28, 29] In the post-operative setting, persistent or increased TR is one of the causes of right-sided heart failure.[29] Theoretically, TA should better preserve right ventricular function post-operatively and in the long-term. However, the relation between right heart failure en TR severity is still incompletely understood. Some suggest that TR is caused by right ventricular failure rather than vice-versa.[30] Indeed, we observed higher TR severity and lower right ventricular function in patients undergoing additional TA. This would mean that repairing tricuspid competence does not restore ventricular function. However, others have shown favourable remodelling of the right ventricle after TA, especially in patients with severe TR preoperatively.[12, 13] We now add to this evidence with an improved event-free survival, probably due to better preservation of right ventricular function when the tricuspid valve is concomitantly repaired.

Lastly, 32% of patients undergoing concomitant TA had a tricuspid annulus diameter >40 mm or >21 mm/m^2 as assessed by echocardiography. The better survival

observed in this patient population therefore is an indication for an even more liberal approach towards TA. It seems to us, that current cut-off values for tricuspid annular dimensions are quite conservative and it seems obligatory to integrate several parameters in the decision process in this difficult patient population. The exact indication for performing simultaneous TA remains difficult to determine, exactly because of this multi-causality.

Conclusion

These data provide evidence on the clinical benefit to perform TA in conjunction with MVS. The heart team should be alerted for TR progression during follow-up and if any doubt about the necessity, performing tricuspid annuloplasty seems to be the wiser decision. As TA will be performed more readily, more insights in which patients the tricuspid valve can be left alone will probably emerge.

Limitations

Our results are based on a retrospective analysis of patients followed in a single institution. However, this resulted in accurate data of the studied patients and propensity matching tried to eliminate surgical selection bias.

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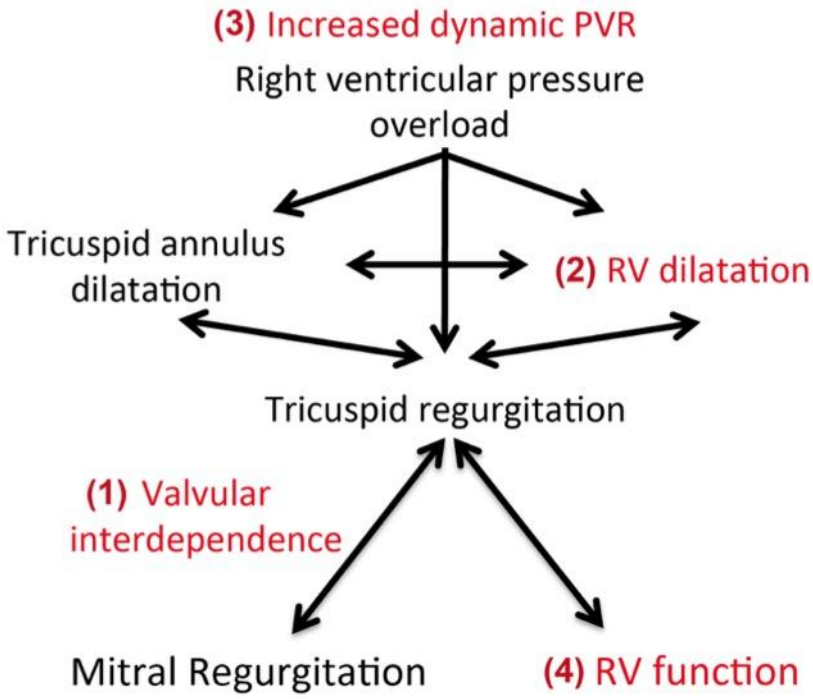
General discussion

1. Summary of Key results

1.1 Tricuspid regurgitation: different determinants and complex interactions

Secondary or functional TR is associated with different types of heart disease. We evaluated the pathophysiology of TR as described in literature and added new determinants from analyses we have done. A summarizing diagram of the pathogenesis of TR is depicted in **Figure 1**. Each type of cardiac pathology presents with specific disease characteristics in which TR originates from a complex interplay of determinants, all of them to a different extent contributing to the pathophysiology.

Figure 1 Determinants of secondary TR as reported in literature (black) and investigated in the current thesis project (red).



1.1.1 Valvular interdependence

Mitral valve regurgitation is known to cause functional TR. This is thought to be a consequence of elevated left atrial pressure, leading to venous pulmonary hypertension. However, we found a strong and independent correlation of the degree of mitral valve regurgitation with TR, without increased pulmonary artery pressures.

A possible explanation for this newly found correlation might be the close relation of the MV annulus and the TV annulus, connected to each other by the fibrous trigonum, part of the valvular cytoskeleton. From a mechanical point of view, mitral valve annular dilatation might lead towards disturbances in tricuspid annular geometry, causing secondary TR.

1.1.2 Right ventricular dilatation itself is important in the pathogenesis of TR in the pressure-loaded ventricle.

Increased pressure-load is thought to be the main cause of TR in patients with pulmonary hypertension. However, chronic RV pressure-load causes changes in the morphology and function of the right ventricle. When looking in detail to patients with pre-capillary pulmonary hypertension, we found that the degree of right ventricular remodelling, defined as right ventricular dilatation, is also an independent determinant of TR. This emphasizes the importance of right ventricular dilatation in the pathogenesis of secondary TR.

1.1.3 Increased dynamic pulmonary vascular resistance is associated with persistent TR.

After closure of an atrial septal defect (ASD) type 2, significant right ventricular remodelling occurs. However, right ventricular remodelling does not lead invariably to the resolution of pre-existing TR. We evaluated the increase in pulmonary artery pressure during exercise and found that patients with mild persistent TR after ASD closure present with more increased pulmonary pressures at peak exercise. As a consequence, patients after ASD closure often present with a smaller decrease of PVR during exercise than healthy controls. We hypothesize that persistent pressure load during exercise maintains TR persistence.

1.1.4 Right ventricular function is important to preserve tricuspid valve competence

We evaluated the impact of RV function on TR in patients with a pressure-loaded RV during exercise.

First, although the pressure gradient across a congenital pulmonary valve stenosis during exercise increased linearly with cardiac output, we couldn’t observe an increase in TR severity as assessed by colour Doppler echocardiography. In these patients, RV dimensions and RV function at rest were normal and the cardiac

response to exercise didn't differ from healthy controls. The good response of the myocardium to exercise might explain the lack of increase in TR although RV pressure load was importantly elevated. We concluded that, if the RV is still healthy, no TR occurs in mild to moderate congenital pulmonary valve stenosis.

In addition, we designed a pilot trial to evaluate the impact of decreased contractile reserve on TR severity in patients with repaired tetralogy of Fallot with a pulmonary homograft. During low-dose dobutamine stress MRI, 1/5 patients presented with impaired contractile reserve, as evidenced by a decrease in stroke volume. As hypothesized, we found an increase in tricuspid regurgitant fraction during stress, whereas in patients with a preserved contractile reserve, this phenomenon could not be observed. However, the low number of patients studied does not allow making any firm conclusions.

1.2 Development of TR and right ventricular dysfunction in pre-capillary PH

We analysed incident patients with pre-capillary PH for the impact of TR on outcome. TR at baseline was associated with worse prognosis. Moreover, the development of severe TR during follow-up was associated with a 2-fold increased risk of death. This indicates the importance of development of TR in the follow-up of patients with pre-capillary PH. In addition, by evaluating consecutive measurements of right ventricular function, we were able to identify right ventricular deterioration predictive for the development of TR during follow-up. Hence, right ventricular function is already deteriorating at the time severe TR develops. The added volume-load at the time of TR progression probably causes a vicious circle, with further deterioration of RV function and eventually death. These findings confirm the importance of right ventricular deterioration prior to development of severe TR.

1.3 Exclusion of pulmonary hypertension: a predictive model, with integration of right heart morphology and TR severity.

In an attempt to simplify exclusion of pulmonary hypertension, we evaluated whether a score of simple echocardiographic parameters (right atrial dilatation, right ventricular dilatation and TR severity) would be able to offer an alternative for measurements of tricuspid regurgitant velocities or pulmonary artery acceleration

time. Furthermore, we validated this score with right heart catheterization in a subgroup of patients.

We found that our newly developed model could reliably exclude patients with pulmonary hypertension in a low risk population. Patients who present with a score <3 wouldn't need additional investigation to exclude pulmonary hypertension. On the other hand, if the score is ≥3, invasive pressure measurements are advocated. We believe that this scoring model would be a fast and easy way to screen low risk populations for pulmonary hypertension.

1.4 Isolated tricuspid valve surgery: when is it time to intervene?

Short and long-term results of isolated TV surgery were evaluated in our centre. In the studied patient cohort, post-operative and long-term mortality was high and comparable to other reported contemporary series. We found that patients presenting in NYHA functional class II or I had excellent post-operative and long-term outcome. On top of this, the presence of pulmonary hypertension before surgery was associated with worse outcome. We hypothesize that isolated TV surgery has the best outcome when symptoms are limited and pulmonary hypertension is lacking.

Table 1 Pre-operative parameters associated with worse outcome after surgery for tricuspid valve regurgitation as reported in literature. Predictors found in our study cohort are indicated in red.

Demography	**Functional**	**Morphology**	**Invasive**	**Biochemistry**
- Age	- NYHA	- RV dilatation	- Mean PAP	- Hgb
- Male gender	- Diuretic treatment	- RV ESA (≥20cm2)		- Renal failure
	- RV function (RIMP)			
		- TV tethering area		- Liver cirrhosis
		- RA dilatation		- Albumin

RV=right ventricle; RIMP=right index of myocardial performance; ESA=end-systolic area; TV=tricuspid valve; RA=right atrium; Hgb=hemoglobin.

1.5 Concomitant tricuspid valve annuloplasty at the time of mitral valve surgery: an opportunity to improve patient outcome?

Controversy exists whether the tricuspid valve should be repaired at the time of left-sided valvular disease. Although current guidelines advocate a more liberal approach towards concomitant tricuspid valve annuloplasty at the time of valvular surgery, the clinical benefit of this intervention has not been proven.

A major confounder in patients undergoing tricuspid valve repair at the time of mitral valve surgery is the inherent selection bias. The decision to perform additional tricuspid valve surgery is made by multidisciplinary consultation, which often leads towards performing surgery in patients with higher TR severity, higher NYHA functional class, more dilated right ventricles, and more signs of impaired right ventricular function.

By implementing a propensity score, we eliminated this selection bias in our studied cohort of patients. We found that patients undergoing concomitant tricuspid annuloplasty at the time of mitral valve surgery had better event-free survival for the combined end-point of cardiac mortality and hospitalisation for heart failure.

2. Clinical applicability and future perspectives

The integration of the different etiological determinants seems to be key in the evaluation of TR. The m**orphometric changes of the right ventricle influence the occurrence TR.** In patients with pre-capillary PH, negative right ventricular remodelling, dilatation and decreased RV function are important predictors of the occurrence of TR. Building on these morphometric changes observed, an **exclusion score for elevated pulmonary pressures** was developed.

The implementation of such a scoring could be used as part of large-scale population-based screening. The function of the tricuspid valve contributes importantly to the scoring process.

In pre-capillary PH, the pressure-load on the RV is often high and leads to important RV dilatation and a more spherical RV. Separation of the papillary muscles is further accentuated by systolic bowing of the interventricular septum towards the left ventricle with increased tension on the septal TV chordal insertions. This leads to

important leaflet tethering and consequently, TR. Lastly, as RV dysfunction develops, a further increase in TR occurs. **Right ventricular function** seems to be a key factor in the pathogenesis of TR. When the ventricle is healthy, it is able to withstand the increased pressure-load during exercise, whereas RV dysfunction during exercise could cause increased TR. Likewise, in patients with pre-capillary PH, **development of severe TR was preceded by progressive right ventricular dysfunction**. Therefore, RV function and RV function relative to pulmonary artery pressure should be systematically evaluated during the follow-up of patients with pre-capillary PH. In summary, TR is predominantly determined by morphometric and functional changes of the right ventricle due to the increased pressure-load.

Although the determinants of TR in left-sided heart disease are largely similar, the pathway of TR occurrence may be different. Elevated pulmonary artery pressures secondary to left heart disease lead to changes in RV morphology and function. However, left-sided heart disease is also associated with LV dilatation and dysfunction. Because of ventricular interdependence, the left ventricle has also an effect on both morphology and function of the RV. The resulting TR then accelerates the underlying disease process. Furthermore, we showed that the function of both atrioventricular valves are closely linked to each other. This may be an additional pathway in the pathogenesis of TR, especially in left-sided valvular disease. Many studies have indicated that tricuspid valve disease can occur late after mitral valve surgery. The concept of **valvular interdependence** emphasizes both atrioventricular valves should be evaluated simultaneously. This concept might also be important in the planning of mitral valve surgery. The effect of annuloplasty and the degree of annular reduction in mitral valve surgery might have important consequences with regards to occurrence of late TR. *We believe that further study should investigate the mechanical relationship of the mitral and tricuspid annulus.*

An **impaired dynamic PVR response to exercise** after surgical correction of an ASD2 late in life is associated with persistent mild TR. More elevated pulmonary artery pressures during daily activities can lead to subtle morphological changes of the TV apparatus. *Future follow-up should evaluate if these changes lead to progression of TR severity in long-term follow-up or to worse prognosis compared to patients who had their ASD closed early in life. Future follow-up of these patients*

might indicate if TR is progressive compared to patients who had their ASD closed early in life.

The development of severe TR **impacts survival** in patients with pre-capillary PH. Acute TR in patients after tricuspid valvectomy because of tricuspid valve endocarditis showed that the sudden volume-load on the right heart is tolerated for some time. In contrast, patients with TR due to progressive remodelling of the right heart represent a population with advanced myocardial disease. An added volume-load by TR on an already damaged/remodelled ventricle will therefore accelerate RV dysfunction in the presence of increased pressure-load.

Because of the irreversibility of elevated RV pressure-load in patients with pre-capillary PH, surgery of the TV is not indicated. Concordant with this, we found that in **isolated tricuspid valve surgery**, PH was associated with worse prognosis. Careful evaluation of potential reversibility of PH pre-operatively is therefore important, as irreversible PH leads to unsatisfactory surgical results. Furthermore, severe symptoms of heart failure also lead to high mortality post-operatively. Earlier referral for isolated tricuspid valve surgery is therefore indicated. To evaluate this, a multi-disciplinary consultation by a "heart valve team" is important. In addition, in surgery for **mitral valve regurgitation**, concomitant tricuspid annuloplasty leads to improved outcome. An evaluation of all patient parameters remains of the utmost importance and if any doubt about whether tricuspid annuloplasty should be performed, a low threshold towards concomitant repair seems to be appropriate and safe.

In pre-capillary PH, preservation of right ventricular form and function, by targeting the underlying disease, is important in preserving tricuspid valve function and improving outcome. When RV function deteriorates, the patient is at risk of developing severe TR, which is associated with worse outcome. Progressive lowering of indices of RV function and the development of severe TR could be indications for dose adjustment of targeted therapy. In this, the evaluation of RV fibrosis due to the chronic hemodynamic load might also play a role.

Likewise, in functional TR secondary to left-sided heart disease, prevention of negative remodelling, preservation of right ventricular function and geometry, and preservation of the low-pressure/low impedance pulmonary arterial system should be

attempted in clinical follow-up. Earlier surgery, before negative remodelling has occurred might be indicated and is already suggested in current guidelines. Hemodynamic consequences of the increased volume-load, increased left atrial volume and occurrence of pulmonary hypertension, are increasingly recognized indications for surgery. Such approach might prevent TR occurrence in long-term follow-up. Still, the risks of surgery should be carefully weighted with regards to the benefits.

It might be interesting to perform exercise tests in patients undergoing mitral valve surgery with or without tricuspid annuloplasty. Persistence, early or late progression of TR might all be linked with impaired contractile reserve pre-operatively.

Prospective studies should evaluate the impact earlier referral and careful pre-operative assessment of pulmonary hypertension on outcome. Future study should further try to identify those patients that truly benefit from tricuspid annuloplasty.

Thesis abstract

Tricuspid regurgitation (TR) is frequently encountered in the routine cardiology practice. Although mild TR is not considered pathological, increasing TR severity is independently associated with impaired prognosis. Furthermore, post-operative results for TR are unsatisfactory.

We have shown in different studies, both descriptive and experimental, that TR originates due to right ventricular (RV) dilatation, tricuspid annular dilatation and RV pressure load, sometimes in the setting of increased dynamic pulmonary vascular resistance. RV remodelling seems to play an important role in this. Also, the close anatomical relationship between the tricuspid and mitral valve annulus might contribute to the development of TR. Furthermore, especially in the pressure-loaded right ventricle, ventricular function seems to play a key role and development of TR has an important impact on prognosis.

To improve outcome in patients undergoing tricuspid valve surgery, we identified pre-operative functional state as an important predictor. Also, when the patient presents with increase pulmonary artery pressures, outcome is impaired. Currently, it seems that patients are operated too late, when significant impairment and end-organ damage already occurred. Patients with pulmonary hypertension should be evaluated carefully on the reversibility of the elevated pulmonary pressures. Therefore, we advise earlier referral for tricuspid valve surgery.

Similarly, we evaluated the added effect of tricuspid valve annuloplasty at the time of left-sided valve surgery and showed improved clinical outcome in patients undergoing concomitant tricuspid valve annuloplasty.

Experimental validation of the effect of right ventricular function on the pathogenesis of tricuspid regurgitation has been initiated and the effect of different types of mitral valve surgery on the tricuspid valve is under investigation.

Summary

The heart consists of a “low-pressure” (right-sided) chamber, pumping deoxygenated (“blue”) blood towards the lungs and a “high-pressure” (left-sided) chamber, providing oxygenated (“red”) blood to the muscles and organs of the body. In contrast to the valves at the left side of the heart, the tricuspid valve, located at the right side, is less well studied. Hence, it is often referred to as “the forgotten valve”. Tricuspid valve regurgitation can be best described as a “leaky” valve, which causes part of the blood to be pumped backwards rather than forwards. Recent study has revealed that patients presenting with tricuspid valve regurgitation have a worse prognosis. Surprisingly, mortality after tricuspid valve surgery is high, although tricuspid valve repair is technically relatively easy.

In this thesis project, we focussed on the elements that cause tricuspid regurgitation. Furthermore, we evaluated which factors are associated with worse prognosis after surgery and when surgery of the tricuspid valve is indicated.

Although tricuspid valve regurgitation can occur because of a single disturbance of the morphology or function of the heart, we showed that it originates most often by a combination of factors. If the primary cause of tricuspid regurgitation is not well addressed, this can cause adaptations of both the structure and function of the heart, further aggravating the severity of tricuspid valve regurgitation. This way a vicious circle is started, which eventually leads to signs of breathlessness and decreased exercise capacity.

During exercise, the heart increases its blood flow to provide the necessary oxygen to the muscles. In this situation, the heart is acutely stressed, with increasing pressures in the heart. We showed that, if the heart muscle functions normal, no increase in tricuspid valve regurgitation occurs despite this increased load. However, if the heart muscle is not able to respond to exercise appropriately, an increase in tricuspid valve regurgitation is seen. This was also confirmed in patients with chronically increased pressures at the level of the right heart. In these patients, we found that a progressive deterioration of the function of the heart muscle eventually leads to tricuspid valve regurgitation.

With this in mind, the question is raised if we can improve prognosis of patients with tricuspid valve regurgitation. We found that if patients undergo surgery early, the

outcome is excellent, whereas in patients that have already severe symptoms of breathlessness and decreased exercise capacity, we might be too late. On the other hand, if we can intervene in the disease process early, the vicious circle can be broken. Therefore, we evaluated whether patients undergoing surgery of the left-sided valves would have benefit of simultaneous intervention on the tricuspid valve, although only mild disease might be visible. In these patients, we found indeed improved outcome if the tricuspid valve was addressed as well.

Taken together, our findings show that tricuspid regurgitation is a disease that can occur in a number of clinical scenario's, each with their own combination of risk factors for disease progression. Close evaluation of the patient is of the utmost importance to evaluate whether surgery is indicated or not. If so, one should not hesitate to perform early surgery.

Samenvatting

Het hart bestaat uit 2 hartkamers. De rechtszijdige hartkamer werkt aan lagedruk en pompt het zuurstofarme (“blauwe”) bloed naar de longen. De linkszijdige hartkamer werkt onder hoge druk en ontvangt het zuurstofrijke (“rode”) bloed van de longen en pompt deze naar de spieren en organen van het lichaam. Voor de goede werking van het hart zijn er verschillende kleppen in het hart aanwezig, die ervoor zorgen dat het bloed in de juiste richting gepompt wordt. In tegenstelling met het kleppensysteem aan de linkerkant van het hart, werd er naar de “tricuspidalisklep”, die zich aan rechterkant van het hart bevindt, weinig onderzoek gedaan. Er wordt daardoor vaak naar de tricuspidalisklep gerefereerd als “the forgotten valve”.

Indien de tricuspidalisklep onvoldoende afsluit, wordt een deel van het bloed de verkeerde richting uitgestuurd. Dit fenomeen wordt “tricuspidalisklep insufficiëntie” genoemd. Recente studies hebben aangetoond dat patiënten die zich presenteren met tricuspidalisklep insufficiëntie een slechtere prognose hebben. Daarnaast merken we in de klinische praktijk dat patiënten die geopereerd worden voor tricuspidalisklep insufficiëntie, soms blijvend klachten hebben van kortademigheid. Dit is enigszins verrassend, aangezien tricuspidalisklep herstel technisch relatief gemakkelijk is.

In dit onderzoeksproject, hebben we de verschillende elementen die tricuspidalisklep insufficiëntie veroorzaken in detail onderzocht. Daarnaast zijn we nagegaan welke factoren de slechte uitkomst van chirurgisch ingrijpen verklaren om zo te kunnen identificeren wanneer chirurgie aangewezen is.

Alhoewel tricuspidalisklep insufficiëntie kan ontstaan door een geïsoleerde verandering van de morfologie of functie van het hart, konden wij aantonen dat het voornamelijk de combinatie van factoren is die uiteindelijk de ernst van de ziekte verklaart. Als de primaire oorzaak van tricuspidalisklep insufficiëntie niet goed behandeld wordt, geeft deze aanleiding tot veranderingen ter hoogte van zowel de structuur, als de functie van het hart. Deze veranderingen kunnen dan op hun beurt aanleiding geven tot tricuspidalisklep insufficiëntie en zo ontstaat er een vicieuze cirkel, die uiteindelijk leidt tot de symptomen van kortademigheid en verminderde inspanningscapaciteit.

Als we een inspanning leveren, dient het hart de hoeveelheid bloed die het rondpompt op te drijven, om er zo voor te zorgen dat er voldoende zuurstof naar de spieren gaat. In deze situatie wordt het hart acuut belast, en verhoogt de druk in de hartkamers. In theorie zou dit aanleiding kunnen geven tot een toenemend lek op de kleppen. We konden echter aantonen dat, indien de hartspier normaal functioneert, geen toename van het lek op de kleppen optreedt. Daartegenover staat echter dat er een toename van de ernst van de tricuspidalisklep insufficiëntie wordt gezien indien de hartspier (beperkte) schade vertoont, en zo onvoldoende kan reageren op de verhoogde eisen die een inspanning vraagt. Dit werd eveneens bevestigd in een patiëntengroep die een chronisch verhoogde druk ter hoogte van de hartkamers hebben. In deze patiënten konden we een progressieve achteruitgang van de hartspierfunctie vaststellen die uiteindelijk leidde tot ernstige tricuspidalisklep insufficiëntie.

De vraag kan dan ook gesteld worden of we de prognose van patiënten met tricuspidalisklep insufficiëntie kunnen verbeteren. In de bestudeerde patiënten konden we echter vaststellen dat patiënten die vroeg in het ziekteproces chirurgie ondergingen, een uitstekende prognose hadden. Daartegenover staat dat we vermoedelijk te laat zijn om chirurgie voor te stellen bij patiënten die reeds uitgesproken klachten van kortademigheid of een verminderde inspanningscapaciteit hebben. Indien we echter vroeger kunnen tussenkomen in het ziekteproces, kan de vicieuze cirkel gebroken worden. Aanvullend evalueerden we patiënten die chirurgie ondergingen van een linkszijdige klep. We keken na of het tegelijk uitvoeren van een herstel van de tricuspidalisklep bij deze patiënten een voordeel zou bieden, ook al was er enkel milde ziekte aanwezig op het moment van chirurgie. In deze patiënten vonden we inderdaad betere uitkomst als de tricuspidalisklep tegelijkertijd aangepakt werd.

Samenvattend kunnen we besluiten dat tricuspidalisklep insufficiëntie een ziekte is die kan ontstaan in verschillende klinische situaties, die elk hun eigen combinatie van risicofactoren hebben voor ziekteprogressie. Om de indicatie voor chirurgie duidelijk te maken is het belangrijk om de reden van de tricuspidalisklep insufficiëntie te identificeren. Indien chirurgie aangewezen is, is een snelle interventie aangewezen.

Curriculum Vitae

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Publications

Articles in internationally reviewed academic journals)

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